MEDIUM EFFECTS ON THE STEREOCHEMISTRY OF EPOXIDE RING-OPENING

MASASHI INOUE

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GENERAL SURVEY

Epoxides are important raw materials in chemical industry.[1] In synthetic chemistry, they are versatile intermediates which react with various nucleophiles to give α,β-difunctional compounds.[2] In biochemistry, they play important role in metabolism of many organic compounds. Recently,[3] arene oxides are watched with keen interest, because they have been demonstrated to be formed in metabolic paths of carcinogenic polycyclic aromatic hydrocarbons.[4] Thus, it is significant to understand the factors governing the epoxide reaction.

From the viewpoint of synthetic chemistry, there are two major problems in epoxide reactions, *i.e.* stereoselectivity and regioselectivity of the reaction. In basic conditions, nucleophiles attack the least substituted carbon atom of epoxide exclusively with inversion of configuration at the carbon atom attacked. On the other hand, the reactions under acidic conditions show always low regio- and stereo-selectivities because of many unknown factors affecting the selectivities. This thesis deals with the reaction paths of epoxides under acidic conditions, especially with the medium effects on the stereochemistry of the reaction.

This thesis is composed of two parts outlined as follows. The first part contains four chapters, dealing with the reaction of epoxide with aluminum chloride and some related

reactions.

Chapter I describes the stereochemistry of ring-opening of aliphatic epoxides with aluminum chloride. The reactions in nitro compound solvents gave chlorohydrins with retention of configuration, while those in many other solvents gave the products with inversion of configuration. The experimental results show that the stereochemistry of the reaction is related to aluminum chloride-solvent 1:1 addition compounds, and the reported data has been explained in terms of the structure of aluminum chloride in solution. For the first time, it is shown that the structures of aluminum chloride in solution are intimately connected with the stereochemistry of the reaction.

Chapter II describes the regioselectivity of the reaction of epoxides with aluminum chloride and salt effects on the reaction. It is demonstrated that the solution structures discussed in Chapter I also affect the regioselectivity of the reaction.

Chapter III describes the Friedel-Crafts reaction with epoxides. Solvent effects on the reaction of anisole with propylene oxide have been examined, and it was found that the reaction in nitromethane gave 1,1-bis(methoxyphenyl)-propanes without any contamination of 1,2-isomers. Various kinds of epoxide also yielded 1,1-bis(methoxyphenyl)alkanes. It is concluded that the isomerization of epoxide to aldehyde followed by condensation with anisole yields the products.

Chapter IV describes the Friedel-Crafts reactions of benzene with 1,2-dihalopropanes (closely related compounds to propylene oxide), allyl alcohol, 2-phenyl-1-propanol, 1-phenyl-2-propanol, and their derivatives. The reactions gave mixtures composed of 1,1- and 1,2-diphenylpropanes, propylbenzene (reduced product), and 1,1-diphenylpropene (oxidized product). A mechanism which can explain all the results reported so far is proposed. Although it is well known that oxidation-reduction reactions take place as side reactions of Friedel-Crafts reaction, no report has described the formation of simple olefin (1,1-diphenylpropene) as an oxidation product except two recent papers, and the observation seems to give a clue to clarify the mechanism of the reaction and to control the side reaction of industrially important alkylation reaction.

Part II is composed of four chapters and deals with the solvent effects on the stereochemistry of acid-catalyzed solvolysis of 2,3-diphenyloxirane (I), an aryl substituted ethylene oxide.

Chapter V describes the ethanolysis of (I) in binary solvent mixtures composed of ethanol and co-solvents. When highly polar and weakly basic co-solvents such as acetonitrile and sulfolane are used, relative yield of the retained product vs. the inverted product increased in solvent mixture containing more co-solvent, while solvent systems containing DMSO and HMPA which have high polarities afforded

larger amounts of inverted product; moderately basic or inert co-solvents have slightly retentive effects. The mechanisms of co-solvent effects on the stereochemistry of solvolytic reactions are reviewed and it is pointed out that these mechanisms cannot explain the results of the ethanolysis of (I). The solution shell concept by Gurney has been introduced to explain the results successfully.

Chapter VI presents the experimental results of the temperature effects on the acid-catalyzed ethanolysis of (I), discusses the mechanism which has been proposed for acid-catalyzed solvolytic reaction of aryl epoxides and arene oxide in the literature, and proposes a more plausible mechanism.

Chapter VII describes the co-solvent effects on the acid-catalyzed hydrolysis of (I) and demonstrates that the results can be explained by the mechanisms discussed in Chapters V and VI.

Chapter VIII discusses the product distributions and the stereochemistry of solvolysis of (I) in a binary solvent system of ethanol-water.

The solvation shell concept introduced in Chapter V assumes the microscopic structure of the solution containing charged species. Region A is a primary coordination sphere in which solvent molecules are highly ordered by the influence of the charged species, region C is a region of unaltered bulk solvent, and region B is a compromise one.

The co-solvent effects described in Chapters V and VII can be explained by considering the probabilities of existence of solvent molecules in region A and B; in region A, the probability of existence of more basic solvent is higher, and in region B, the probability of more polar solvent is higher than that which can be expected from the proportion of the whole solvent system. Thus, effective concentrations of nucleophilic solvent are different in regions A and B. These differences of the concentrations determine the stereochemistry of the reaction.

This discussion is not limited to the epoxide reaction and may be extended to the usual acid-catalyzed solvolytic reactions.

Throughout this thesis, the author has demonstrated that the solvent effects on the stereochemistry of acid-catalyzed reaction cannot be explained only by the solvent polarity which is widely accepted to explain the reaction kinetics, and that the basicity of solvent is very important as well as the polarity to discuss the effects on stereochemistry. He also pointed out the importance of microscopic consideration of the solution structure around the reaction center, and suggested the possibility of the stereochemical control by the choice of solvent.

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Masashi Inoue

CONTENTS

PART I

REACTION OF EPOXIDE WITH ALUMINUM CHLORIDE AND RELATED REACTIONS

CHAPTER I Solvent Effects on Stereoselectivities of Ring-Opening Reaction of Epoxide with Aluminum Chloride

The ring-opening reaction of 2,3-epoxybutane with aluminum chloride yielding 3-chloro-2-butanol was examined in several different solvents. The reaction proceeds with 94% retention of configuration in nitromethane solvent. The retentive ring-opening was observed to variable extents when nitro compounds, ethers, and aromatics were utilized as the solvents, but a complete inversion resulted in the other solvents. The structure of aluminum chloride in various solvents is discussed, and aluminum chloride-solvent 1:1 addition compounds in solution are concluded to be important for the retentive ring-opening.

1 Introduction

Ring-opening reactions of epoxides with nucleophiles are generally accompanied with inversion of configuration at the point of attack, and can be explained by S_N2 mechanism.[1] Reactions which proceed with retention of configuration have been reported in some cases of phenyl and acyl substituted epoxides. A double inversion mechanism with neighboring groups and a four centered

mechanism with an ion-pair have been proposed for these reactions.[2-5] Parker and Isaacs proposed that the reactions which proceed with racemization take place not by S_N1, but by concurrent S_N2 and S_Ni mechanisms.[1]

Yielding chlorohydrins by the reaction of epoxides with aluminum chloride is well known not only as a side reaction of Friedel-Crafts reaction, but also as a modification of catalyst in cationic polymerization of epoxides. It was reported that an alkyl substituted epoxide, epoxypropane, afforded a chlorohydrin with a retained configuration in a reaction with aluminum chloride in nitromethane (NM) solution.[6] In this chapter, the author wishes to report the solvent effects on the stereoselectivities of the ring-opening reaction of epoxide with aluminum chloride.

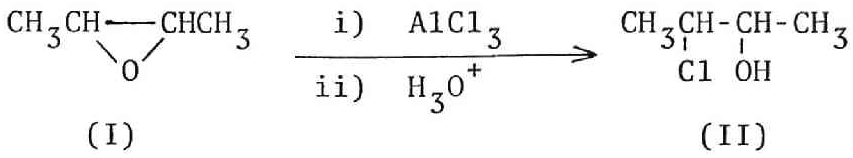
2 Results and Discussion

The ring-opening reaction of *cis*- and *trans*-2,3-epoxybutanes (I) with aluminum chloride, yielding *erythro*- and *threo*-3-chloro-2-butanols (II), was examined in several different kinds of solvents. The stereochemical results are summarized in Table 1. It was also confirmed that the stereochemistry of the products was not affected in the course of hydrolysis of the produced aluminum alkoxides, since no ^{36}Cl was introduced into the product when the reaction mixture was hydrolyzed with aqueous $H^{36}Cl$.

Table 1. Stereochemistry of ring-opening reaction of 2,3-epoxybutane with $AlCl_3$[a]

Solvent	(I)	Reaction temperature[b] °C	(II) Yield %	Steric course Retention %
Carbon disulfide	*cis*	0	15.0	0
Chloroform	*cis*	0	42.3	0
Acetonitrile	*cis*	0	38.1	0
Acetone	*cis*	0	4.6	0
Ethanol	*trans*	0	76.1	0
Nitromethane (NM)	*cis*	−10	24.1	94
Nitromethane	*cis*	0	12.7	85
Nitromethane	*cis*	18	13.2	36
Nitromethane	*cis*	27	10.6	25
Nitromethane	*trans*	−11	18.5	93
Nitromethane	*trans*	0	13.8	80
Nitromethane	*trans*	24	12.3	30
Nitromethane + Chloroform[c]	*trans*	0		65
1-Nitropropane	*trans*	0	24.1	59
2-Nitropropane	*trans*	0	30.3	49
Nitrobenzene	*trans*	0	14.4	48
Benzene	*trans*	7	5.9	trace
Toluene	*trans*	0	3.8	0.6
Mesitylene	*trans*	0	1.4	2.8—4.9
Ethyl ether	*trans*	0	16.5	52
Anisole	*trans*	0	4.2	2
Diphenyl ether	*trans*	28	8.3	0
DMSO	*trans*	0	4.6	0
DMF	*trans*	0	7.8	0
Sulfolane	*cis*	27	17.0	trace
Sulfolane + 1,2-Dichloroethane[d]	*cis*	0		0[g]
Dimethyl sulfone + 1,2-Dichloroethane[e]	*cis*	0		0
Pyridine-*N*-oxide + Chloroform[f]	*cis*	0		3
Triethylamine	*cis*	0	42.5	0

a) Reactions were carried out in 8 ml of the solvents unless specified otherwise on 4 mmol scale of (I) with 1.5 equiv. of $AlCl_3$ for 2 h. b) Cooling bath temperature. c) (I) (4.88 mmol), $AlCl_3$ (5.59 mmol), NM (4 ml) and $CHCl_3$ (4ml). d) (I) (2.80 mmol), $AlCl_3$ (5.60 mmol), sulfolane (39.4 mmol), and $ClCH_2CH_2Cl$ (4 ml). e) (I) (5.30 mmol), $AlCl_3$ (5.48 mmol), $(CH_3)_2SO_2$ (100 mmol), and $ClCH_2CH_2Cl$ (20 ml). f) (I) (4.35 mmol), $AlCl_3$ (5.07 mmol), C_5H_5NO (17.0 mmol), and $CHCl_3$ (10 ml). g) Nakajima reported that the ring-opening reaction of 1,2-epoxypropane with $AlCl_3$ proceeds with 12 % retention of configuration in a mixed solvent of sulfolane and 1,2-dichloroethane.[7]



(I) (II)

The solvents in which the reaction proceeds with retention of configuration are limited to aromatics, ethers, and nitro compounds. The product corresponding to the retention of configuration predominated only in the solvents of nitro compounds.

The ring-opening of (I) with $AlCl_3$ was carried out in carbon disulfide containing variable amounts of NM. In Fig. 1, the percentages of retention are plotted against the amounts of NM added. Nearly linear correlations between the amounts of NM added and the percentage of retention are observed in the regions NM / $AlCl_3$ < 0.5 and NM / $AlCl_3$ > 4. From the intersection of these two straight lines, values of NM / $AlCl_3$ = 1.4 and 1.8 are obtained for *cis*- and *trans*-(I) respectively. This fact seems to indicate that the ring-opening is connected with the 1:1 addition compound of $AlCl_3$ and NM, although the possibility of the participation of the 1:1.5 or 1:2 addition compound cannot be completely excluded. On the other hand, it has been reported that nitroalkanes and many aromatic nitro compounds react with $AlCl_3$ to form crystalline solids generally with the formula of $AlCl_3 \cdot RNO_2$, but also, in a few cases, that of $AlCl_3 \cdot 2RNO_2$.[8a)]

The substituent effects of *p*-substituted nitrobenzenes

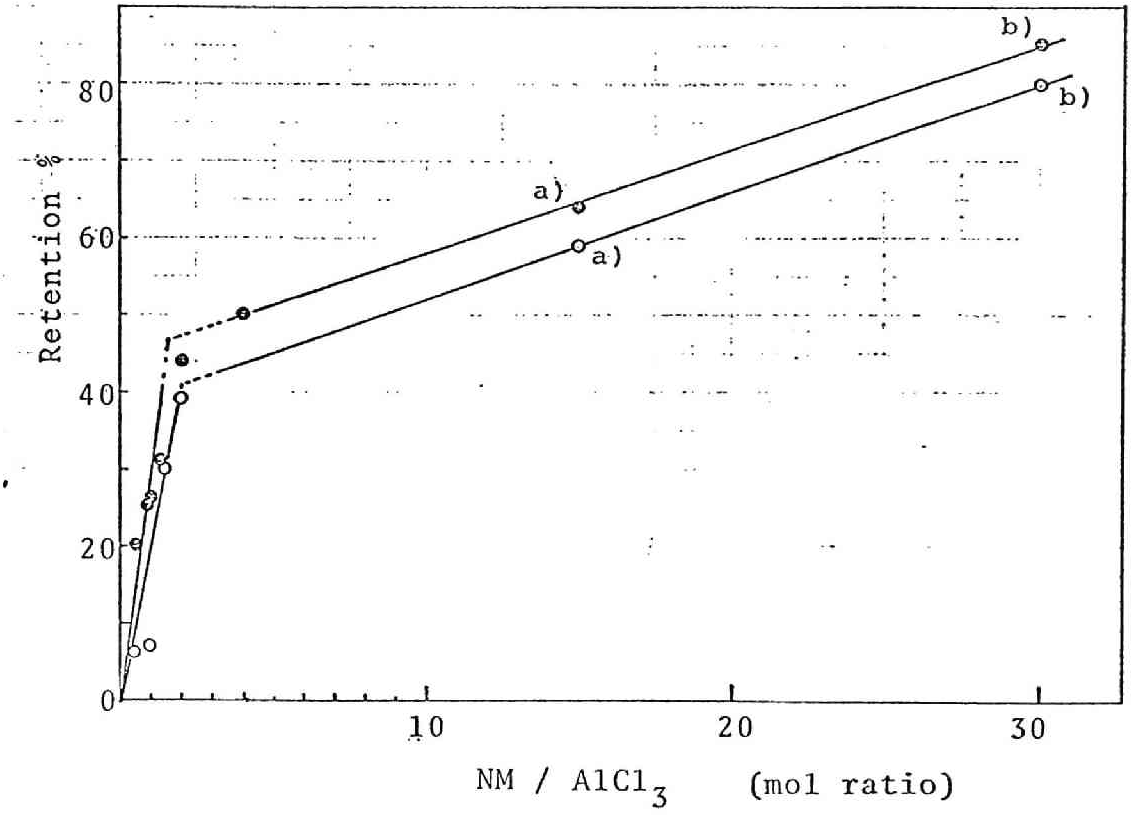


Fig. 1. Plot of CH_3NO_2 / $AlCl_3$ *vs.* stereochemistry of ring-opening reaction of 2,3-epoxybutane: ● , *cis*-(I); ○ , *trans*-(I).

Reactions were carried out in carbon disulfide (8 ml) at 0 °C. An equivalent amount (4 mmol) of $AlCl_3$ to (I) was used. a) Neat NM (4 ml) was used as a solvent. b) Neat NM (8 ml) was used as a solvent.

were investigated in order to account for the specificity of nitro compounds; the results are shown in Table 2. Within the nitro compounds which are soluble in 1,2-dichloroethane, a good correlation is obtained between the percentages of retention and the σ_p-σ_m values of the substituents. This fact indicates that the resonance between π-electrons of an aromatic ring and a nitro group is very significant in the retention process. On the other hand, the σ_p-σ_m values should reflect the stabilities of the 1:1 addition compounds, of which structural information has been reported by Gagnaux.[9] Thus, the more stable 1:1 addition compound, $AlCl_3$·Sv (III, Sv = solvent), increases the retentive ring-opening reaction.

p-Cyano-, *p*-hydroxy-, and *p*-aminonitrobenzenes are insoluble in 1,2-dichloroethane, and the reaction systems are heterogeneous. A nonpolar solvent capable of undergoing homogeneous reaction was searched for in vain. The reaction is accompanied with almost complete steric inversion when these nitrobenzenes were added. In these cases, the group coordinating to aluminum may be not nitro but cyano, hydroxyl, or amino group, even if these compounds form complexes with $AlCl_3$.

The proportions of the retention slightly increase in the order of: benzene < toluene < mesitylene, although the Friedel-Crafts reactions occur predominantly in these solvents. It is still less certain that $AlCl_3$ interacts

TABLE 2. STEREOCHEMISTRY OF RING-OPENING OF 2,3-EPOXY-BUTANE WITH $AlCl_3$ IN THE PRESENCE OF NITROBENZENE DERIVATIVES (p-X-C_6H_4-NO_2)[a)]

X	Stereochemistry Retention %	Hammett σ_p-σ_m
H[b)]	60	-
CH_3[b)]	61	-0.109
Cl[b)]	65	-0.146
OCH_3[b)]	75	-0.383
CN[c)]	0	+0.100
NH_2[c)]	1.3	-0.49
OH[c)]	2.4	-0.82

a) Reactions were carried out using *cis*-(I) in 1,2-dichloroethane containing nitrobenzene derivatives (1.0 M) at 0 °C; $AlCl_3$ / (I) = 1.0-1.4, nitrobenzene derivatives / $AlCl_3$ = 8.6-8.9. b) Reaction was homogeneous. c) Reaction was heterogeneous.

with aromatic hydrocarbon, but there has been evidence of weak complex formation from solubility measurements.[8b,10] Roberts[11] reported that the susceptibility toward aluminum chloride-induced rearrangement of propyl side chains decreased in the series of propylbenzene, propyltouene, and propylxylene. He attributed this to the postulate that the catalyst is progressively less active due to complex formation with aromatics with increasing Lewis basicities. In the present case, the percentage of retention is also proportional to the stability order of the aluminum chloride complexes to be formed.[12]

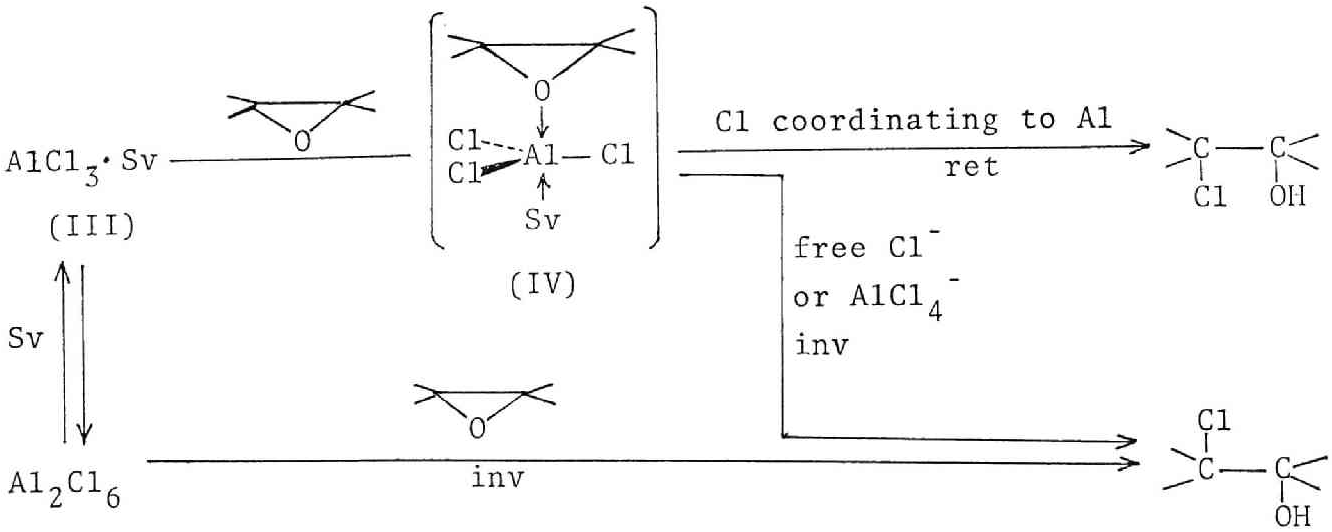
The same conclusion can be drawn from a series of aliphatic nitro compounds. It is well known that the steric effects have an important influence on the stability of 1:1 complexes of Lewis acids and bases.[13] Brown[14] reported that the stabilities of the 1:1 complexes of boron trifluoride and ethers decreased in the order of $Me_2O \cdot BF_3$ > $Et_2O \cdot BF_3$ > i-$Pr_2O \cdot BF_3$.[15] The stabilities of the complexes of $AlCl_3$ and nitro compounds are expected as $MeNO_2 \cdot AlCl_3$ > n-$PrNO_2 \cdot AlCl_3$ > i-$PrNO_2 \cdot AlCl_3$. The sequence is actually consistent with the observed order of the percentages of retention.

In the earlier reports on the ring-opening reactions of epoxides which proceeded with retention of configuration, the mechanism was discussed in the following terms: 1) a double inversion with the participation of neighboring

groups, and 2) a four-centered or an ion-pair mechanism. The mechnism 1) was proposed for the case of phenyl- and carbonyl-substituted epoxides,[2,3,5] and it is, however, improbable for an alkyl substituted epoxide in the present case. The mechanism 2) was proposed by Wasserman and Aubrey[5] as a possible explanation of the results of the reaction of dypnone oxide with hydrogen chloride. Brewster[4] also supposed an ion-pair in a solvent "cage" to explain the *cis* ring-opening of *trans*-α-methylstilbene oxide with acetic acid. An analogous mechanism, shown in Scheme 1, seems to be applicable to the present case.

Solvates of the different composition are known for $AlCl_3$ containing from one to six donor molecules per molecule of $AlCl_3$. Solvents of weak coordinating affinity give 1:1 addition compounds, and those of better coordinating properties give 1:1, 1:1.5, or 1:2 compounds, while 1:4 or 1:6 compounds are limited only to some powerful coodinating solvents. A solvate of the $AlCl_3 \cdot Sv$ type was regarded as an acceptor solvate,[16] since it is capable of accepting further solvent or other donor molecules.

On the addition of epoxide, the solvated aluminum chloride (III) may accept lone-pair electrons of epoxide and be transformed into complex (IV).[17] The collapse of (IV) gives chlorohydrin of a retained configuration whose chlorine comes from the coordinating site to aluminum. On the contrary, the inverted product can be derived by the


AlCl3· Sv
(III)
Sv
Al2Cl6
Cl
Cl
Al
Cl
Sv
(IV)
Cl coordinating to Al
ret
free Cl-
or AlCl4-
inv
inv
C
C
Cl
OH
Cl
C
C
OH

Scheme 1.

attack of free chloride ion in the solution on the solvated complex (IV). An analogous mechanism involving a common intermediate leading to both of *cis* and *trans* oxymercurials was recently proposed by Bach and Richter.[18] Furthermore, in the present case, the solvated complex (III) may be equilibrated with aluminum chloride dimer. Aluminum chloride is well-known to exist as a dimer in carbon disulfide or in chloroform. Since a chlorohydrin with an inverted configuration is obtained in these solvents, the reaction of epoxide and Al_2Cl_6 is considered to proceed with inversion. In the system involving stable addition compounds, the equilibrium should lie towards the complex (III) rather than the dimer; that is, the more stable addition compounds afford an increased amount of the chlorohydrin with a retained configuration.

If the ring-opening of epoxide with $ALCl_3$ is assumed to follow Scheme 1, free ion species and also the dimer should not exist in the system which yields a chlorohydrin with a retained configuration. However, an inconsistency inheres in this condition. To satisfy the condition, the solvent must be moderately basic; free chloride ion may be formed by cleavage of Al-Cl bonds if the solvent basicity is too strong.

In order to discuss the effect of a free ion, the ring-opening reaction of (I) was pursued in NM by the addition of lithium salts as a source of free ions.

The results are tabulated in Table 3. The reaction process alters from retention to inversion by the addition of an equivalent amount of lithium chloride. In the experiments using $Li^{36}Cl$, the produced (II) contained 22.6% of radioactivity. This result indicates that all the chlorines of lithium chloride and $AlCl_3$ are equivalent within the limits of experimental error. The addition of lithium chloride creates an equilibrium:

$$AlCl_3 \cdot Sv + LiX \underset{}{\overset{Sv}{\rightleftharpoons}} LiSv_n^+ + AlCl_3X^- \quad (2)$$

The anion $AlCl_4^-$, formed in this equilibrium attacks epoxide, and the reaction proceeds with inversion of configuration.[19]

A mechanism involving the back-side shielding by a solvent may be expected, but it is inadequate for the present system by the facts that a high retention of configuration is observed only in nitro compound solvents, and that the reaction proceeds with complete inversion in acetonitrile which exhibits a good back-side shielding effect in solvolysis.[20] The substitution reaction of epoxides under acidic condition was claimed not to proceed by the A1 mechanism, but by the borderline A2 mechanism,[21] even in a system stabilizing the carbonium ion such as styrene oxide.[22] It was also reported that the rearrangement of epoxide to carbonyl compounds does not occur through a planar carbonium ion, but occurs in a more concerted manner.[23] The temperature effect on the stereoselectivity shown in Table 1

TABLE 3. STEREOCHEMISTRY OF RING-OPENING OF 2,3-EPOXYBUTANE WITH $AlCl_3$ IN NITROMETHANE. EFFECTS OF THE ADDITIONAL LITHIUM HALIDE

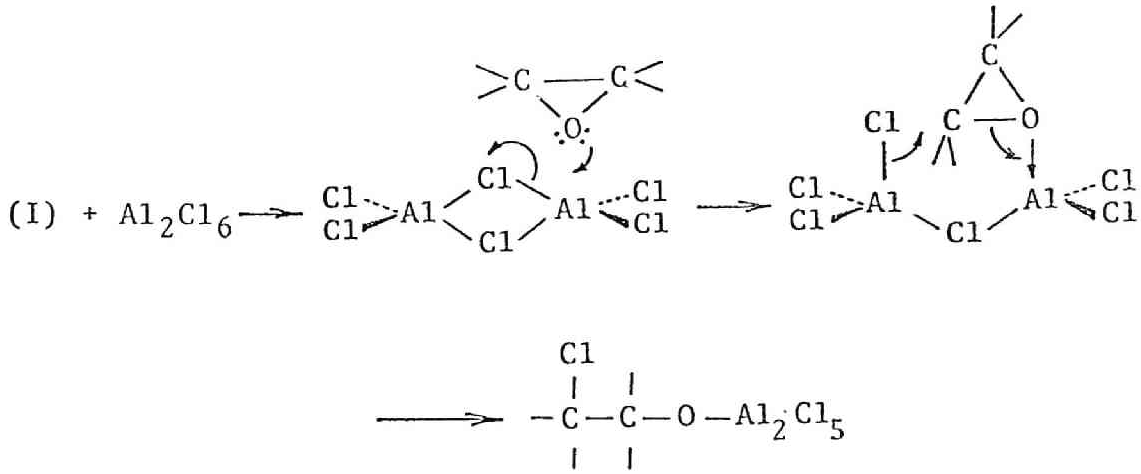
Lewis acid (mol ratio)	Stereochemistry Retention %
$AlCl_3$	85
$AlCl_3$ + LiCl (1:1)	6
$AlCl_3$ + HCl (1:1)	3
$AlCl_3$ + HCl (1:0.03)	72
$AlCl_3$ + LiBr (1:1)	2[a)]
$AlBr_3$ + LiCl (1:1)	1[a)]
(LiCl)	no reaction
(LiBr)	no reaction

a) The product was 3-bromo-2-butanol containing a trace of (II).

seems to constitute evidence for the arguments against the intermediacy of the fully developed carbonium ion. If the ring-opening in NM proceeds *via* the carbinium ion – back-side shielding mechanism, the ratio of racemization would increase at higher temperatures. At 27 °C, the result is 25% retention and 75% inversion, which means 50% inversion and 50% racemization. As inversion and racemization at 18 °C are 28 and 72% respectively, an inversion process prevails at higher temperatures. The observed temperature effects cannot be explained by assuming the formation of a carbonium ion. These results suggest a larger activation entropy and enthalpy for the reaction accompanied with steric inversion than for the reaction with retention. Taking a cyclic transition state, the S_Ni reaction can be expected to have a smaller activation enthalpy and a larger negative value of activation entrophy than the S_N2 reaction. The observed temperature effect is explicable by assuming the S_N2 mechanism for the ring-opening reaction with inversion and the S_Ni mechanism for the reaction with retention. However, the differences in the relative rates due to the reaction temperature are too large to be accounted for by only the competition of S_N2 and S_Ni reactions. These differences may also be due to an equilibrium between the addition compound ($AlCl_3 \cdot Sv$) and the dimer (Al_2Cl_6), as is indicated in Scheme 1.

The ring-opening reaction proceeds with inversion of

configuration in nonpolar solvents, such as carbon disulfide and chloroform, in which aluminum chloride is dimeric. In these solvents, however, it is difficult to assume a free ionic species which attacks the coordinated epoxide in (IV) from the back-side. Therefore, it seems to be difficult to explain an inversion mechanism by a model for the transition state at a single metal atom center. A mechanism which involves two separate metal sites has been proposed by Price for the triethylaluminum-water catalyzed epoxide polymerization, which proceeds with inversion of configuration at the carbon atom undergoing ring-opening attack.[24] On these bases, a most plausible mechanism for the ring-opening of epoxide with the dimer Al_2Cl_6 in nonpolar solvent is depicted in scheme 2.[25]



Scheme 2.

Many studies have been made concerning the structure of $AlCl_3$ in solutions;[26] among them, the investigation by means of NMR appears to be most reliable. The structures of $AlCl_3$ in solution can be classified into the following four groups on the basis of experimental results obtained by NMR techniques:

Type 1. Solutions in which $AlCl_3$ is completely dissociated into ions.

Solutions of $AlCl_3$ in protic and aprotic polar solvents belong to this group. In DMSO[27] and ethanol,[28] Al-Cl bonds are completely dissociated into ions, and aluminum cation is coordinated by six molecules of the solvents.[29]

$$AlCl_3 + 6Sv \longrightarrow AlSv_6^{3+} + 3Cl^-$$

Type 2. Solutions in which disproportionation occurs.

The apparent solvation number of $AlCl_3$ in acetonitrile is 1.5,[30] and the Al-Cl bonds dissociate partially into ions.[28,31,32]

$$4AlCl_3 + 6Sv \longrightarrow AlSv_6^{3+} + 3AlCl_4$$

Type 3. Solutions in which $AlCl_3$ forms 1:1 addition compounds with the solvents

$$AlCl_3 + Sv \longrightarrow AlCl_3 \cdot Sv$$

Although many compounds are reported to form 1:1 addition compounds in the crystalline state with $AlCl_3$, the

existence of the 1:1 compounds in solution has been confirmed in a few cases. Nitro compounds are considered to form the 1:1 adduct in solution.[33,34] Ether and benzene may also form 1:1 adducts in equilibrium state.[28,35,36] The 1:1 adducts are acceptor solvates, as has been mentioned before.

Type 4. Solutions in which $AlCl_3$ exists as a dimer.

Aluminum chloride exists as a dimeric form Al_2Cl_6 in nonpolar solvents such as carbon disulfide and chloroform.[37] Ether and benzene are considered to contain the dimer Al_2Cl_6 under equilibrium with the 1:1 adducts.[28,36]

The ring-opening of epoxide with $AlCl_3$ proceeds with retention of configuration only in the solvents of Type 3. In mixed solvents, the one with the stronger ability to coordinate to aluminum determines the nature of the solution; *e.g.*, the structures of $AlCl_3$ in the mixed solvents of Types 1 and 2, and of Types 2 and 3 are dominated by the solvent natures of Types 1 and 2 respectively. When an equivalent amount of NM to $AlCl_3$ is added to acetonitrile solution, the structure of $AlCl_3$ in the solution is Type 2 and the epoxide ring opens with 100% inversion. This results is in good contrast with that of the reaction carried out in carbon disulfide solution containing NM.

Haraguchi reported the order of coordination affinity against aluminum as H_2O > EtOH ≫ I > Br > Cl > PhCN > CH_3CN.[28,36] If lithium halide is added to the solution of Types 2 and 3, aluminum in the solution will mostly be in the state of

$AlCl_3X^-$, since the halogen has a stronger affinity than the solvent does. In these systems the reaction proceeds with inversion.

The structure of $AlCl_3$ in solution affects not only the stereospecificity but also the regiospecificity of the ring-opening reaction of epoxides with $AlCl_3$, as is discussed in the next chapter.

3 Experimental

The vlpc analyses were carried out on Hitachi K-53 and Shimazu 3AH gas chromatographs, and vlpc preparation was carried out on an Aerograph Auto-prep A-700 chromaograph.

Materials. *cis*- and *trans*-Epoxybutanes (I) were prepared by the method of Pasto and Cumbo.[38] Vlpc analysis (a 45 m polypropylene glycol Ucon oil LB-550X capillary column was employed) indicated the *trans*-(I) to be free from any *cis*-isomer, whereas *cis*-(I) accompanied 1.4% of the *trans* isomer. All the solvents were dried by the most efficient ways appeared in the literature[39] and were distilled before use. Commercial special grade aluminum chloride was purified by sublimation three times under a reduced pressure before use. Lithium chloride and bromide were dried over P_2O_5 at 140 °C in vacuum.

A Typical Procedure of Ring-Opening Reaction. Into a solution of $AlCl_3$ (0.877 g, 6.58 mmol) in 4 ml of acetonitrile,[40] (I) (0.318 g, 4.69 mmol) in 4 ml of acetonitrile

was slowly added under well-stirring in an ice bath. It took 2 h for the addition at a constant temperature, and stirring was continued for an additional 30 min. After the duration, the reaction mixture was poured into a mixture of 10 ml of concd HCl and 50 g of ice. The organic layer was separated and washed with 20 ml of water. The combined aqueous layer was saturated with NaCl and extracted twice with 30 ml and then with 20 ml of ether. The combined organic layer was dried over Na_2SO_4 after the addition of mesitylene as an interal standard. The solvent was evaporated off, and the residual product was submitted to vlcp analysis. *erythro*-3-Chloro-2-butanol (II) was obtained in 38% yield based on (I), and neither *threo*-(II) nor the unreacted (I) was detected. The product was identified by a comparision of the vlpc retention time with those of the authentic samples.[41] The product could be converted into *trans*-(I) with dil. NaOH.

Vlpc Analyses. The Vlpc analyses were carried out on Hitachi K-53 gas chromatograph. The retention times of *threo*- and *erythro*-(II), *threo*- and *erythro*-3-bromo-2-butanols, and mesitylene were 7.4, 8.9, 13.7, 15.7, and 10.4 min respectively on a 2 m column packed with 25% tricresyl phosphate and 1.5% H_3PO_4 on Chamelite CK at a column temperature of 100 °C.

^{36}Cl Tracer Experiment. The radioactivity mesurements were performed by means of a Packard Tri-Carb liquid

scintillation spectrometer model 3380. Radioactive lithium chloride was prepared from lithium carbonate and 1 N $H^{36}Cl$, and was dried at 140 °C in vacuum until the weight is constant.

The crude (II) obtained by the reaction was purified by means of preparative vlpc (Carbowax-20M 20%, 20 ft column), and submitted to measurments of radioactivity. A solution of PPO (4g) and dimethyl-POPOP (0.1 g) diluted with toluene to 1.0 l was used as the scintillator. The radioactivities of $H^{36}Cl$ and $Li^{36}Cl$ were measured in homogeneous solutions prepared by the addition of small amounts of ethanol or ethanol and water. Quenching corrections were carried out with the use of an external standard channel ratio method. The results of the experiments were summarized in Table 4.

The author is especially indebted to Drs M. Hamada and R. Kiritani, Radiation Center of Osaka Prefecture, where the radioactive tracer experiments were carried out.

TABLE 4. RESULTS OF ^{36}Cl TRACER EXPERIMENTS OF RING-OPENING REACTION OF 2,3-EPOXYBUTANE WITH $AlCl_3$ IN NITROMETHANE SOLVENT

Entry	Sample (mmol)	Automatic external standard ratio	dpm	dpm/mmol
1	Blank	0.8777	47.0	
2	(II) (0.292)[a]	0.8817	63.9	
3	$H^{36}Cl$ (1.94×10^{-3})	0.6604	2839.9	1473.7×10^3
4	(II) (0.0534)[b]	0.8965	43.1	807.1
5	$Li^{36}Cl$ (0.0292)	0.6959	14465.8	495404
6	(II) (0.183)[c]	0.8718	20481.3	111920

a) An authentic non-active sample. b) The product obtained by hydrolyzing the non-active reaction mixture with $H^{36}Cl$ specified in entry 3. $AlCl_3$ (15.58 mmol), $H^{36}Cl$ (4.85 mmol) ^{36}Cl/total Cl = 9.40%. c) The product obtained by the reaction with $AlCl_3$ (15.25 mmol) and $Li^{36}Cl$ (entry 5; 15.29 mmol); ^{36}Cl/ total Cl = 25.2%, ^{36}Cl taken into (II)/total ^{36}Cl = 22.6% (= 111920/495404).

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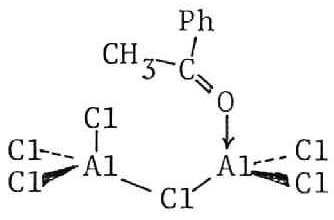

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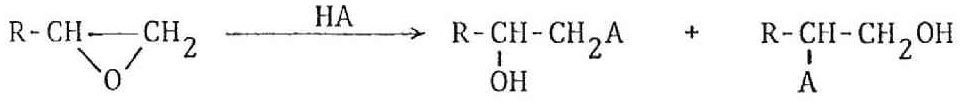
CHAPTER II Solvent Effects on Orientation of Ring-Opening Reaction of Epoxide with Aluminum Chloride

The ring-opening reaction of 1,2-epoxypropane with aluminum chloride was examined in various solvents. The composition of the produced 1-chloro-2-propanol and 2-chloro-1-propanol was strongly affected by the solvent. The latter was exclusively produced in nitromethane, though the former predominated in several other solvents. When lithium bromide was added, different amounts of bromopropanols were obtained together with chloropropanols, and the product distributions were related to the structures of aluminum chloride in solution.

1 Introduction

Much have been written regarding the ring-opening reaction of epoxides. Nevertheless, the orientation of the ring-opening is still a rather confused subject. When unsymmetrically substituted epoxides are involved, ring-opening can occur in either of two different directions:



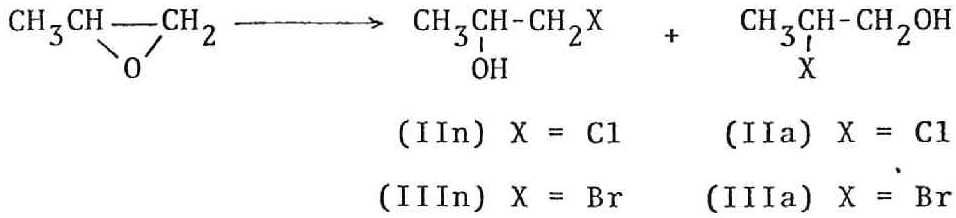
Normal product Abnormal product

In general, the reaction to cleave the bond between less substituted carbon and oxygen is termed "normal ring-opening", while the other direction is termed "abnormal".[1] In the case of base-induced reactions, normal ring-opening is predominant, but acid-catalyzed substitution reactions usually give considerable amounts of the abnormal products.

The preceding chapter reported that the stereochemistry of the ring-opening of 2,3-epoxybutane with aluminum chloride is strongly affected by the changes of the structure of aluminum chloride in solution. In this chapter solvent effects on the orientation of ring-opening of epoxide with aluminum chloride will be reported and discussed in terms of the structure of aluminum chloride in solution.

2 Results and Discussion

The reaction was carried out by slow addition of 1,2-epoxypropane (I) to aluminum chloride in various solvents. After hydrolysis, the products were analyzed by vapor phase chromatography. The isomer distributions of the produced chloropropanols (II) are summarized in Table 1.



(IIn) X = Cl (IIa) X = Cl

(IIIn) X = Br (IIIa) X = Br

In contrast with the fact that normal ring-opening is

TABLE 1. RING-OPENING REACTION OF 1,2-EPOXYPROPANE WITH $AlCl_3$ IN VARIOUS SOLVENTS[a)]

Solvent	Yield (II) (%)	Product ratio (%)	
		(IIn)	(IIa)
CS_2	54.0	47	53
$ClCH_2CH_2Cl$	71.0	17	83[b)]
Et_2O	26.3	57	43
CH_3NO_2	51.6	2	98
CH_3CN	97.5	87	13
EtOH	96.4	91	9
DMSO	18.7	81	19

a) Experimental condition; (I):$AlCl_3$:solvent = 1:1:50.

b) The proportion of (IIa) depended upon the rate of addition of (I), and it decreased until a minimum 18% when (I) was added rapidly.

predominant in acetonitrile (AN), ethanol, and dimethyl sulfoxide (DMSO), the proportion of the abnormal ring-opening product (IIa) increased in ether, carbon disulfide, and 1,2-dichloroethane. Furthermore, an extensive abnormal ring-opening as much as 98% was observed in nitromethane (NM). A few reactions are known which proceed with more than 90% abnormal ring-opening. In these cases, nucleophiles preferably attack the hindered carbon atom.

The preceding chapter discussed on the structure of $AlCl_3$ in solution, and showed that solvents can be classified into four types. In polar solvents such as DMSO and ethanol, $AlCl_3$ is completely dissociated into ions, and aluminum cation is solvated by six molecules of the solvents (Sv) (Eq. 2)

$$AlCl_3 \longrightarrow AlSv_6^{3+} + 3Cl^- \qquad (2)$$

The second type of solvents is the moderately basic solvents such as AN. Aluminum-chlorine bonds are partially dissociated into ions in these solvents (Eq. 3).

$$4AlCl_3 + 6Sv \longrightarrow AlSv_6^{3+} + 3AlCl_4^- \qquad (3)$$

Solvents of the third type form 1:1 adducts with $AlCl_3$ in solution (Eq. 4), to which nitro compounds and ethers are

$$AlCl_3 + Sv \longrightarrow AlCl_3 \cdot Sv \qquad (4)$$

included. Nitro compounds, especially NM, which showed an extraordinary character in the stereochemistry of the ring-opening, also show an extensive abnormal ring-

opening, as is shown in Table 1. The last type is nonpolar solvents where $AlCl_3$ is considered to exsist as a dimer.

The results summarized in Table 1 suggest that these differences of the structure of $AlCl_3$ in solution also opperate substantially on the change of orientation of the ring-opening.

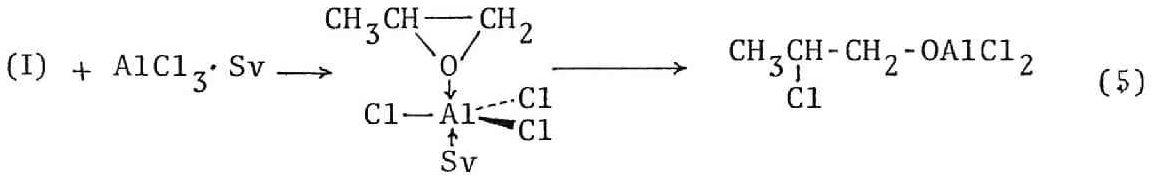
Although several different mechanisms have been called into play to explain the divergent results of ring-opening reactions of epoxide, a consistent explanation can be given in terms of a "push-pull" mechanism.[2] Because of the strain in the three-membered ring of epoxide, the cleavage of the C-O bond will be important, especially in acid-catalyzed reactions, in which proton or Lewis acid coordinates to the epoxide oxygen. The coordination of these acids provides a strong pull in the displacement. As a result, steric factors are less influential than usual.

The ring-opening of aliphatic epoxide with $AlCl_3$ in NM cannot be considered to involve a fully developed carbonium ion because of the stereochemical results mentioned in Capter I. As the 1:1 adduct of $AlCl_3$ and NM is an acceptor solvate and can coordinate on the epoxide oxygen, favorable bond-breaking may occur between secondary carbon and oxygen giving the abnormal product (IIa).

Such mode of reaction is often observed in the substitution reactions of heterocyclic compounds.[3]

For example, the Friedel-Crafts reaction of (I) proceeds with inversion of configuration, accompanied with a complete abnormal ring-opening.[4] The ring cleavage of cyclic sulfate has been considered to proceed by S_N1 mechanism under acidic conditions, because the reaction of unsymmetrical cyclic sulfate from 1,3-butanediol with hydrochloric acid takes place on the secondary carbon.[5] However, the ring-opening of the cyclic sulfate of 2,4-pentanediol with hydrochloric acid proceeds with complete inversion of configuration, yielding 4-chloro-2-pentanol.[6]

As has been postulated in Capter I, $AlCl_3 \cdot Sv$ is the reacting species in NM and ether solutions, and the chlorine atom of the products comes from the coordnation sphere of



(5)

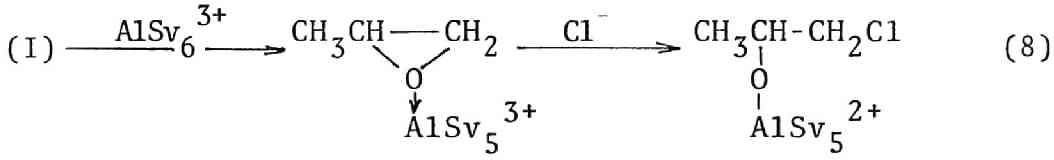
aluminum (Eq. 5). In DMSO, ethanol, and AN, on the contrary, chloride and $AlCl_4^-$ ions play an important role in the nucleophilic substitution of epoxide. The dissociated aluminum cation is completely solvated, fulfilling its coordination number, and it seems no longer to provide the strong pull by coordination of the epoxide oxygen.

It has also been reported that the ring-opening reaction of (I) with hydrochloric acid proceeds concurrently by the two paths shown in Eqs. 6 and 7.[7] The analogous

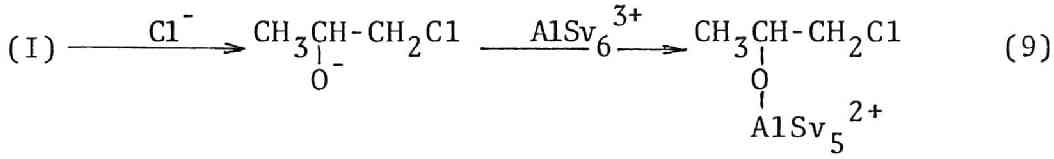
course can be considered for the reaction of (I) with $AlCl_3$ in polar solvents (Eqs. 8 and 9).

(6)

(7)



(8)



(9)

The nucleophiles produced in DMSO and ethanol are bared and solvated chloride ions respectively, but $AlCl_4^-$ ion is the nucleophile in AN.[8] Equation 8 may be considered as a usual acid-catalyzed reaction via an onium ion, and Eq. 9, as a reaction with a base. It is well known that base-induced ring-opening reaction of epoxide exclusively results in the normal ring-opening. As the normal product (IIn) is favored in DMSO, ethanol, and AN, the respectable part of the ring-opening reaction in these solvents is expected to proceed by means of Eq. 9.[9]

The regioselectivity of the ring-opening reaction appears to depend upon the counterbalance of the pull by Lewis acids and the push by nucleophiles. The result that the normal product predominates in the polar solvents

may reflect the weak pull by $AlSv_6^{3+}$ cation and the strong push by chloride or $AlCl_4$ ions. This is in good contrast with the results of the Friedel-Crafts reaction, in which a bulky and weak nucleophile, benzene, provides only weak push, while $AlCl_3$ pulls very strongly; thus, the result is a complete abnormal ring-opening, as has been mentioned before.

To confirm these considerations, the effect of added alkali metal halide on the regioselectivity of ring-opening of (I) with $AlCl_3$ was examined.

The results shown in Table 2 can be summarized as follows; 1) the normal ring-opening becomes predominant when the salts are added, and bromides are more effective than chlorides; 2) the bromopropanols (III) predominate when bromides are added, except in the cases of sodium and potassium bromides in ether; 3) the difference of cation has little influence on the product compositions.

Quite different regioselectivity was observed when the salts are added in NM and ether solvents; thus, the reacting species are considered to be different in the reactions with and without alkali metal halides. The stereochemistry of the ring-opening reaction of 2,3-epoxybutane in NM turns from retention to inversion by the addition of lithium chloride. When lithium halide is added to the reaction system, $AlCl_3X^-$ ion is formed by the Eq. 10,[10] and the ring-opening reaction is considered to be initiated by the attack

TABLE 2. RING-OPENING REACTION OF 1,2-EPOXYPROPANE IN THE PRESENCE OF SALTS[a)]

Solvent	Addendum	Yield (%) (II)+(III)	Product ratio (%) (IIn)	(IIa)	(IIIn)	(IIIa)
CH_3NO_2	none	48.3	4	96		
CH_3NO_2	LiCl	72.6	62	38		
CH_3NO_2	NaCl	53.3	58	42		
CH_3NO_2	KCl	58.4	73	27		
CH_3NO_2	LiBr	81.5	14	4	69	13
CH_3NO_2	KBr	65.4	15	4	73	8
Et_2O	none	34.8	57	43		
Et_2O	LiBr	37.8	4	1	89	6
Et_2O	NaBr	29.0	61	39	0	0
Et_2O	KBr	33.0	57	43	0	0

a) Experimental condition; (I):$AlCl_3$:addendum:solvent = 1:1:1:50.

TABLE 3. SOLVENT EFFECTS ON THE RING-OPENING OF 1,2-EPOXYPROPANE IN THE PRESENCE OF LITHIUM BROMIDE[a)]

Solvent	Yield (%) (II)+(III)	Product ratio (%) (IIn)	(IIa)	(IIIn)	(IIIa)
CS_2	36.3	61	34	5	trace
$ClCH_2CH_2Cl$	37.9	44	40	9	3
Et_2O	34.8	21	3	70	6
CH_3NO_2	84.9	11	3	75	11
CH_3COCH_3	92.7	12	1	83	4
CH_3CN	96.1	8	1	86	5
DMF	22.1	63	7	29	1
DMSO	13.8	69	13	17	1
EtOH	80.4	69	8	21	2
EtOH	100	49	6	43	2

a) Experimental condition; (I):$AlCl_3$:LiBr:solvent = 1:1:1:20.

of that ion. It has been reported that AlX_4^- has nucleophilicity to some extent, though it is a weaker nucleophile than halide ion.[11]

$$AlCl_3 \cdot Sv + LiX \underset{}{\overset{Sv}{\rightleftharpoons}} LiSv_n^+ + AlCl_3X^- \quad (10)$$

As is shown in Table 3, the product distribution in AN is similar to those obtained in NM and ether; in these solvents $AlCl_3Br^-$ is a reacting species, but it distinctly differs from those in DMSO and ethanol, in which the added salts completely dissociate into ions. This fact indicates that the regioselectivity is related closely to the anionic species.

If the equilibrium 10 is taken into account, lithium cation should be the acid providing the pull in the Eq. 8, when the solvents of the second and third types are used. Although it has been reported that lithium salts have catalitytic activities in the ring-opening and rearrangement reaction of epoxides,[12] only a weak participation of lithium cation may be displayed by the electrostatic interaction in the present case, since not only lithium but potassium salt is effective and the reaction is not so much affected by the change of cations. As the pull provided by lithium cation may be much weaker compared with that by $AlCl_3 \cdot Sv$, the more normal ring-opening results when the lithium halides are added to NM. When sodium and potassium bromides are added, the equilibrium 10 stays far

to the left in ether, because these salts are insoluble in this solvent. Thus, these salts seem to have no influence on the regioselectivity in an ether solvent.

As affinity of bromide ion to aluminum is stronger than that of chloride,[13] the formation of AlX_4^- species in the equilibrium is more satisfactory when lithium bromide instead of chloride is added. As a result, the more normal ring-opening product is obtained by the addition of lithium bromide.

The results shown in Table 3 can be explained by taking the before-mentioned types of the structure of $AlCl_3$ in solution into account. The first class of solvent, consisting of polar solvents such as DMSO, DMF, and ethanol, can completely dissociate metal-halogen bonds of $AlCl_3$ and lithium salts into ions. In these solvents, metal cations are strongly coordinated by the solvent molecules. The distribution of the halohydrins produced depends upon the nucleophilicities of the halide ions. In aprotic polar solvents, halide ions are not solvated and their nucleophilicities depend upon their basicities, $Cl^- > Br^-$.[14] On the contrary, halide ions are solvated in protic sol vents, their nucleophilicities do not depend upon the basicities, and the order of nucleophilicities has been well established as $Br^- > Cl^-$.[15] Accordingly, the predominant product is (II) in aprotic polar solvents, and the extended proportion of (III) results in protic solvents.

In the moderately basic solvents of the second type, (AN, acetone, etc.), and in NM and ether of the third type, a larger amount of (III) was yielded than was to be expected from the nucleophilicities of halide ions in aprotic solvents. The reaction without the addendum in NM and ether proceeds by scheme 5 where no ionic species are present. An $AlCl_3Br^-$ ion is formed according to Eq. 10 when the lithium bromide is added in solvents of the second and third classes. It is most reliable that the ring-opening is caused by the attack of $AlCl_3Br^-$ instead of free chloride or bromide ions in these systems. However, insufficient evidence is available at this time to interpret the predominant formation of (III) with the use of $AlCl_3Br^-$. One of the most reasonable elucidations for this subject may be offered by Pearson's HSAB principle.[16] Bromine is a softer base within four halogens in $AlCl_3Br^-$, and the carbon atom of epoxide is a soft acid. As a soft acid is favorable to react with a soft base, (III) should be the predominant product of the reaction with $AlCl_3Br^-$.

If the reaction conditions of LiBr / (I) $\geqq$ 1 is satisfied as is shown in Table 4, (III) is the principal product and no difference is observed in the product distributions. The exhaustive formation of (III) in the system of (I) : $AlCl_3$: LiBr = 1:2:1 may be indicative that the reaction rate of $AlCl_3Br^-$ and (I) is faster than that of $AlCl_3 \cdot Sv$ and (I), for the same amount of $AlCl_3 \cdot Sv$ as $AlCl_3Br^-$

TABLE 4. EFFECTS OF MOLE RATIO OF THE REAGENTS ON THE RING-OPENING REACTION[a)]

Mole ratio			Product ratio (%)			
(I)	$AlCl_3$	LiBr	(IIn)	(IIa)	(IIIn)	(IIIa)
1	1	1	7	1	85	7
1	1	0.5	37	9	50	4
1	1	2	2	trace	89	9
1	0.5	1	4	1	87	8
1	2	1	4	2	86	8
0.5	1	1	5	1	84	10
2	1	1	36	8	51	5

a) Solvent: Et_2O (100 mol eq.).

should exist in the system even if Eq. 10 is completely shifted to the right under these conditions.

In the nonpolar solvents which are classified as the fourth type (carbon disulfide, dichloroethane, etc.), the abnormal ring-opening product indicates a tendency to predominate over the normal product. The addition of lithium bromide shows little effects, as is shown in Table 4 and 6. The reactions in these nonpolar solvents are insufficient in the reproducibility and the product distribution was strongly affected by the rate of the addition of (I) to a mixture of $AlCl_3$ and a nonpolar solvent. As $AlCl_3$ is less soluble in these solvents, the reaction was heterogenous initially. When an equivalent amount of (I) had been carefully added, $AlCl_3$ was completely dissolved. When (I) was added rapidly, some portions of $AlCl_3$ were remained as solid at the end of addition of (I), and the proportion of (IIa) was varried from 17 to 82% by the rapid addition. These facts indicate that the ring-opening of (I) with alkoxyaluminum chloride, initially formed by the reaction of (I) with $AlCl_3$, may not be neglected.

Therefore, the reaction of excess amount of (I) with $AlCl_3$ was examined. The composition of the normal ring-opening product (IIn) increased in the order of 17, 27, and 37% with an increase in the mole ratio of (I) / $AlCl_3$ = 1.0, 2.0, and 3.0 in 1,2-dichloroethane. These results indicate that the alkoxyaluminum chloride ($AlCl_2OR$ or

TABLE 5. SOLUTION STRUCTURE OF $AlCl_3$ AND THE RING-OPENING REACTION OF EPOXIDES

Type	Solution structure[a]	Solvation number	Typical solvent	Selectivity	
				Stereo	Regio
1	$AlSv_6^{3+}+3Cl^-$	6	DMSO, DMF	inv	nor
1′	$AlSv_6^{3+}+3ClSv_n^-$	6	EtOH	inv	nor
2	$AlSv_6^{3+}+3AlCl_4^-$	1.5	CH_3CN	inv	nor
3	$AlCl_3\cdot Sv$	1	CH_3NO_2	ret	abnor
4	Al_2Cl_6	—	CS_2, $CHCl_3$	inv	mixture

In the presence of lithium bromide

Type	Solution structure[a]	Selectivity		Product
		Stereo	Regio	
1	$AlSv_6^{3+}+LiSv_m^++3Cl^-+Br^-$	inv	nor	(II) > (III)
1′	$AlSv_6^{3+}+LiSv_m^++3ClSv_p^-+BrSv_q^-$	inv	nor	(II) ≧ (III)
2	$AlCl_3Br^-+LiSv_m^+$	inv	nor	(III)
3	$AlCl_3Br^-+LiSv_m^+$	inv	nor	(III)
4	Al_2Cl_6	inv	mixture	(II)

a) Those indicated in italics are the active species of each reaction.

$AlCl(OR)_2$) reacts with (I) to give more (IIn) than in the reaction of $AlCl_3$. The proportion of normal ring-opening seems to increase in the order of $AlCl_3$ < $AlCl_2OR$ < $AlCl(OR)_2$. As the Lewis acidities generally increase by an increase in the electronegativities of X in metal salts MX_n,[17] the Lewis acidities decrease in the order of $AlCl_3$ > $AlCl_2OR$ > $AlCl(OR)_2$. Thus, the normal ring-opening should be favored in the cases of weaker Lewis acid.

In the case of the rapid addition of (I), initially formed $AlCl_2OR$ reacts with (I) before $AlCl_3$ dissolves out into the solvent, and larger amounts of (IIn) were formed than in careful addition. Since the dissolving rate of $AlCl_3$ should be significantly influenced by the nature of crystal of $AlCl_3$ and with mechanical stirring efficiency, the insufficiency of reproducibility appears to be due to these facts.

The results in this chapter can be summarized as Table 5 accompanying those of the stereochemistry of ring-opening presented in the preceding chapter.

3 Experimental

Materials. Commercial 1,2-epoxypropane (I, special grade) was distilled before use. Commercial special-grade aluminum chloride was purified by sublimations three times under a reduced pressure before each use. Lithium chloride and bromide were dried over P_2O_5 at 140 °C in vacuum.

All the solvents were dried by the most efficient ways appeared in the literature[18] and were distilled before use.

A typical Reaction Procedure. To a well-stirred mixture of $AlCl_3$ (1.4 g, 10 mmol) in ether (37.1 g, 500 mmol) was added 0.58 g (10 mmol) of (I) over a period of 20 min in an ice-bath. The stirring was continued for the additional 40 min in an ice-bath. The reaction mixture was poured into 50 g of ice-water. After the duration with stirring, the organic layer was separated, and the aqueous layer was saturated with NaCl and extracted three times with 30 ml of ether. The combined ether extract was dried over Na_2SO_4. After removal of ether, the residual products were submitted to VLPC analysis using tetralin as an internal standard. The yield of chloropropanols was 26.3% (IIn: 43.1%, IIa:56.9%). In this reaction, 1-ethoxy-2-propanol (8.1%) was by-produced, which was identified by the comparisions of the VLCP retention time and the NMR spectrum with those of an authentic sample prepared from (I) and sodium ethoxide, after the product mixture had been treated with dil. NaOH, converting (II) to (I).

A Typical Reaction Procedure in the Presence of Lithium Bromide. In a cold NM (30.5 g, 500mmol), 1.4 g (10 mmol) of $AlCl_3$ was dissolved, then 0.87 g (10 mmol) of lithium bromide was added; the mixture turned to a brown homogeneous solution. To the well-stirred solution, 0.61 g (10.5

mmol) of (I) was added dropwise during a period of 20 min in an ice bath. After a duration of 40 min, the reaction mixture was worked up as mentioned above. The yields of (II) and (III) were 8.6 and 37.8% respectively by VLPC analysis, and the product ratio was; 14.0 (IIn), 4.5 (IIa) 68.6 (IIIn), and 12.9% (IIIa).

It was confirmed that the products composition did not change after they were treated again under the reaction conditions.

Product Anayses. The VLPC analyses were carried out on Hitachi K-53 instrument using a 10% PEG-20M on Celite 545 column (2 m). The retention times of (IIn), (IIa), (IIIn), (IIIa), and tetralin (the internal standard) were 3.2, 3.9, 4.8, 6.1, and 9.1 min respectively at column temperature of 70 °C. These authentic samples were prepared from (I) with corresponding hydrogen halides.[18)]

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9) The first step of equation (8) is regarded as a solvent exchange reaction in which one of the solvent molecule is substituted for the epoxide. Thomas and Reynolds reported the solvent exchange rate of $Al(DMSO)_6^{3+}$ in DMSO.[a)]

$$Al(DMSO)_6^{3+} + DMSO^* \longrightarrow Al^{3+}(DMSO)_5 \cdot DMSO^* + DMSO$$

When reported values are extrapolated to 0 °C, the rate constant

of the reaction at 0 °C is *ca.* 0.001 sec^{-1}. As epoxide is a far weaker base[b] than DMSO,[c] the following exchange reaction should be negligibly slow, which is the first step

$$Al(DMSO)_6^{3+} + CH_3CH\text{-}CH(O) \longrightarrow Al^{3+}(DMSO)_5 \cdot O\langle CH(CH_3)CH_2 + DMSO$$

of equation (8) in DMSO. On the other hand, the reaction of (I) with $AlCl_3$ in DMSO is completed within several minutes. Therefore, the author concludes that the reaction in DMSO proceeds by means of eq. (9). a) S. Thomas and W. L. Reynold, *J. Chem. Phys.*, 44, 3148 (1966). b) S. Searles, Jr., E. F. Lutz, and M. Tamres, *J. Am. Chem. Soc.*, 82, 2932 (1960) c) M. Tamres and S. Searles, Jr., *J. Am. Chem. Soc.*, 81, 2100 (1959). The second step of equation (9) is also regarded as a ligand exchange reaction of solvated complex for alkoxy anion which is reported to be faster than exchange of solvent itself. d) J. E. Akitt, N. N. Greenwood, and G. D. Lester, *J. Chem. Soc., (A)*, 1969, 803; D. Fong and E. Grunwald, *J. Am. Chem. Soc.*, 91, 2413 (1969).

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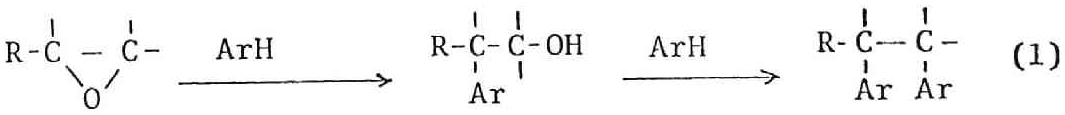
CHAPTER III Aluminum Chloride Catalyzed Friedel-Crafts Reaction of Anisole with Epoxide Accompanying Isomerization[1)]

The reaction of anisole with propylene oxide by aluminum chloride has been studied in various kinds of solvents. While the normal Friedel-Crafts reaction yielded 2-(methoxyphenyl)-1-propanols, 1,1-bis(methoxyphenyl)propanes were also formed in this reaction; these were not obtained by the subsequent reaction of mono(methoxyphenyl) products with another anisole. The yields of 1,1-bis-(methoxyphenyl)propanes increased by increasing the basicity of solvents. The mechanism of the formation of 1,1-bis(methoxyphenyl)propanes can be explained by the isomerization of epoxide to aldehyde and the subsequent condensation with anisole. Various kinds of epoxides also gave 1,1-bis(methoxyphenyl)alkanes in nitromethane.

1 Introduction

It is generally believed that Friedel-Crafts reactions



(1)

of aromatic substrates with epoxides produce β-hydroxyaryl alkanes which react further with aromatics to give 1,2-diarylalkanes (Eq. 1).[2] During the course of the study of solvent effects on the ring-opening reaction of epoxide with aluminum chloride,[3] it was found, however, that the reaction of propylene oxide with anisole by aluminum chloride yielded 1,1-bis(methoxyphenyl)propanes (I) without any contamination of the 1,2-isomers (II). In order to clarify the mechanism, the reaction of various epoxides with anisole has been studied in various solvents.

2 Results and Discussion

The reaction of propylene oxide and anisole without solvent at 0-2 °C gave a complex mixture containing at least eight compounds: 2-chloro-1-propanol (III, 24%), 1-chloro-2-propanol (IV, 8%), 2-(*o*- and *p*-methoxyphenyl)-1-propanols (V, 17%), 1-phenoxy-2-propanol (VI, 4%), and three isomers (*o*,*o*-, *o*,*p*-, and *p*,*p*-) of 1,1-bis(methoxyphenyl)propanes (I, 24%). The first two are the ring-opening products of the epoxide; their isomer distribution and stereochemistry have been discussed in the preceding chapters. The mechanism of the formation of (V), a normal Friedel-Crafts reaction product of propylene oxide, is considered to be of the S_N2 type analogous to the reported case of benzene.[4] In this chapter, however, the author is concerned mainly with the formation of (I).

Table 1 shows the results of the reaction of propylene oxide with anisole in various solvents. For experimental convenience, the yields of the products which did not include methoxyphenyl moiety were not determined. The other products were chloropropanols, oligomers of the epoxide, and high boiling tarry matter. The characteristic features of the results are as follows. When 1,2-dichloroethane was used as a solvent, changes in the reaction conditions resulted in only minor changes in the product distributions. The formation of (II) was not observed in any experiments except one at a higher temperature (32-34 °C). The yield of (I) increased in the following order of the solvents: hexane < chloroform < 1,2-dichloroethane < anisole ≤ nitromethane.

In nitromethane, (I) was obtained in a good yield but no mono(methoxyphenyl) products were detected. This result forms a striking contrast to the fact that benzene does not react with propylene oxide in this solvent.[4] Therefore, the reaction of various epoxides with anisole was examined. Results are summarized in Table 2.

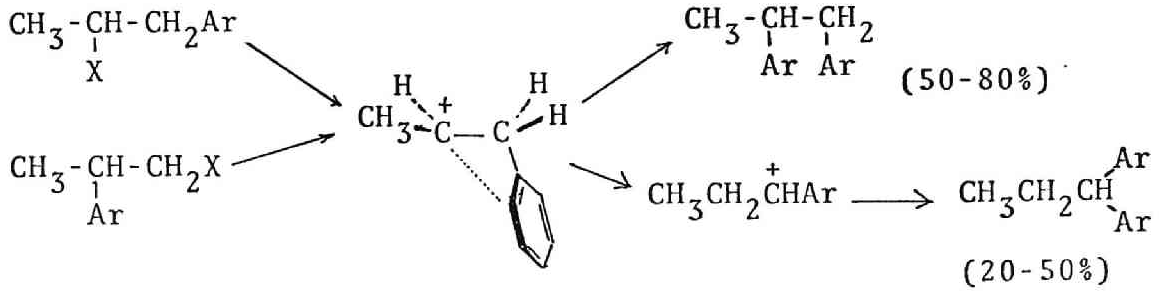
One of the possible routes to (I) is the successive reaction of (V) with another anisole. The literature contains a number of papers on the Friedel-Crafts type alkylation of aromatics with 1,2-difunctional propanes including propylene oxide which gave 1,2-diarylpropanes,[5] while a few papers have reported the formation of 1,1-

TABLE 1. EFFECTS OF THE SOLVENT ON THE REACTION OF PROPYLENE OXIDE WITH ANISOLE.[a)]

Solvent	Yield of(V) %	Yield of(I) %	Isomer distribution in (I) o,o- %	o,p- %	p,p- %
$ClCH_2CH_2Cl$[b)]	8.3	11.3	1.3	24.4	74.3
$ClCH_2CH_2Cl$	5.8	13.4	1.2	24.1	74.5
$ClCH_2CH_2Cl$[c)]	7.4	13.0	0.6	26.5	72.9
$ClCH_2CH_2Cl$[d)]	5.5	11.7	1.0	24.0	75.0
$ClCH_2CH_2Cl$[e)]	10.9	19.3	1.5	27.5	71.0
$ClCH_2CH_2Cl$[f)]	6.1	8.4	0.5	20.0	79.5
$ClCH_2CH_2Cl$[g)]	7.2	14.7	1.0	22.3	76.7
$ClCH_2CH_2Cl$[h)]	4.1	16.2	1.0	26.4	72.6
$ClCH_2CH_2Cl$[i)]	2.5	14.9	(mixture of(I) (80%) and(II)(20%))		
$CHCl_3$	3.2	6.4	1.1	22.7	76.2
$CH_3(CH_2)_4CH_3$	1.3	0.6	1.8	13.2	85.0
CH_3NO_2	0.0	25.8	0.7	12.3	87.0

a) Unless otherwise mentioned, 40 ml of solvent, 20 mmol of epoxide, 40 mmol of anisole, and 20 mmol of aluminum chloride were used. Reaction temperature and time were 0-2 °C and 3.5 hr, respectively. b) Reaction time, 1.0 hr. c) Reaction time, 6 hr. d) Anisole, 20 mmol. e) Anisole, 200 mmol. f) Aluminum chloride, 10 mmol g) Aluminum chloride, 40 mmol. h) Aluminum chloride, 60 mmol. i) Reaction temperature, 32-34 °C.

diarylpropanes as by-products.[6] Masuda *et al.* explained the formation of 1,1-diphenylpropane (minor product) in the reaction of 1-phenyl-2-chloropropane and 2-phenyl-1-chloropropane with benzene in terms of an isomerization from a phenonium ion type intermediate to 1-phenyl-1-propyl cation on the basis of stereochemical results (Scheme 1).[7,8]



Scheme 1

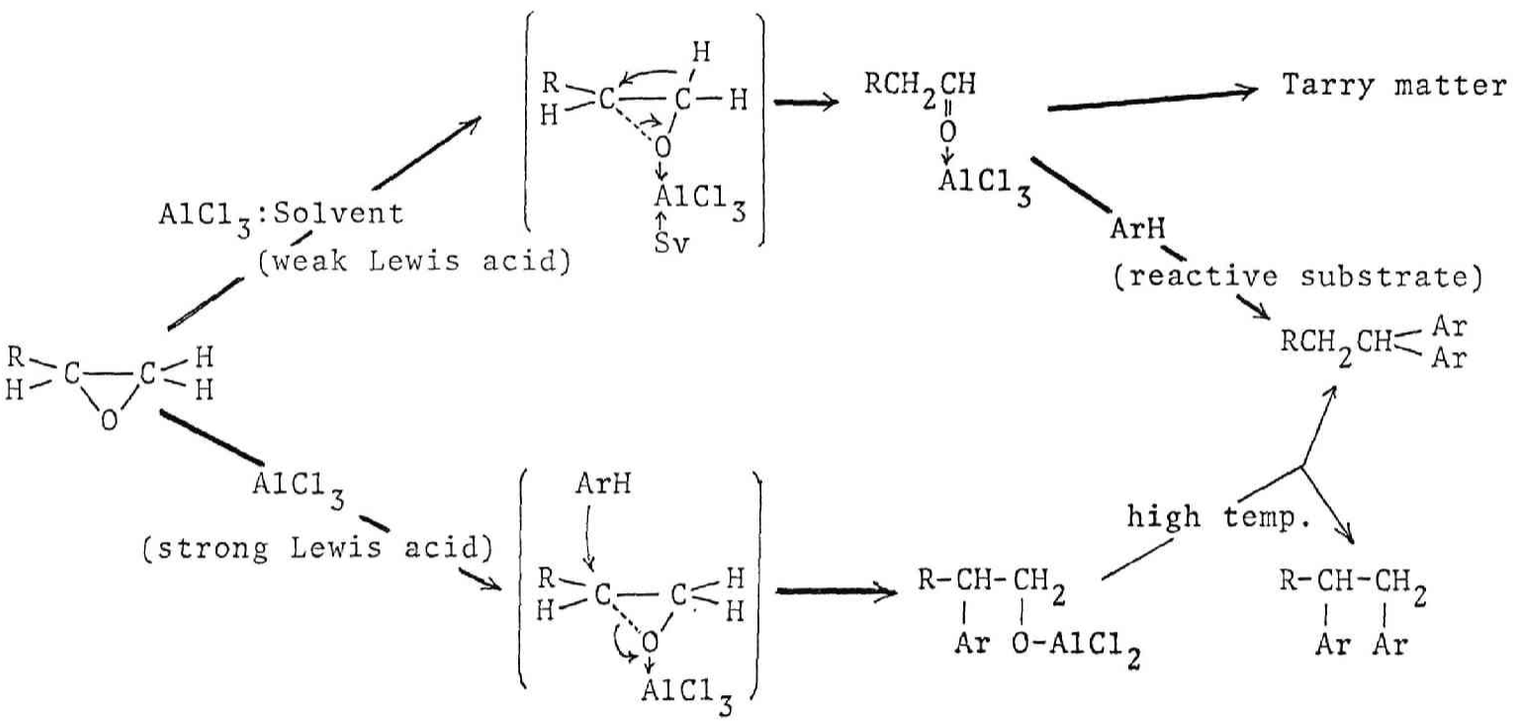
To examine this reaction sequence, (V) was subjected to react with excess anisole in the presence of aluminum cloride at 0-2 °C. The predominant product was (II) (80%), and (I) was only a minor one (20%). Although the data may not reflect exactly the path of the reaction of propylene oxide with anisole, since hydrogen chloride is produced in the reaction of (V) with aluminum chloride to form the assumed precursor, dichloroaluminum 2-(methoxyphenyl)-propoxide, it can be concluded that the main route to (I) is different from this reaction sequence, since the hydride shift from the phenonium type ion to 1-aryl-1-propyl cation

is not affected by the leaving groups of the precursors of the carbonium ion.[8)]

Possible routes for the formation of (I) are shown in scheme 2, in which R is methyl and Ar is methoxyphenyl or phenyl. Isomerization from epoxide to aldehyde, followed by condensation with anisole, leads to (I). The isomerization competes with the normal Friedel-Crafts reaction and the aldehyde condensation with anisole competes with the formation of tarry matter *via* aldol condensation, Tischenko reaction, and so on.

It is well known that epoxide forms aldehyde under the catalysis of magnesium bromide, zinc chloride, and boron trifluoride-ether complex.[9)] These catalysts are weak Lewis acid as compared with aluminum chloride. The acidity of aluminum chloride dissolved in nitromethane is lower than those in the other usual solvents for Friedel-Crafts reactions, since nitromethane is a stronger base than the other solvents. The activity of the catalyst becomes low, and benzene does not react with propylene oxide in this solvent. When more reactive anisole was used as a substrate, the isomerized aldehyde condenses with anisole to form (I). As the basicity of the solvents increases in the order mentioned above, the solvent effects on the formation of (I) can be explained along the same line.

Although the condensation of aldehyde with aromatics is well known,[10)] no detailed study of the reaction with


AlCl3:Solvent
(weak Lewis acid)
AlCl3
(strong Lewis acid)
ArH
(reactive substrate)
high temp.
Tarry matter

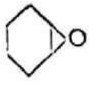
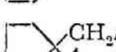
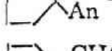
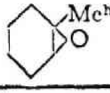
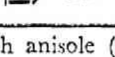
Scheme 2

aluminum chloride catalyst has appeared to our knowledge. The reaction of propionaldehyde with anisole in 1,2-dichloroethane at 0-2 °C in the presence of aluminum chloride gave (I) as a main product (59%), accompanied with 1,1-bis-(methoxyphenyl)propenes (VII, 13%) and 1-methoxyphenylpropanes (VIII, 20%). The formation of the latter two products shows that hydrogen transfer took place; this will be discussed in the following chapter.

The results shown in Table 2 are also well consistent with the mechanistic paths mentioned in scheme 2. The products in runs 8, 9, and 10 indicate that phenyl and alkyl migrations took place instead of hydrogen migration. The products which are not expected from the reaction sequence mentioned above are suggestive for the study of the nature of aluminum chloride catalysis. The formations of (XV) and (XVI) appear to indicate that the splitting of the phenyl or methoxyphenyl group, isomerization, and a hydride attack to an intermediate carbonium ion occurred. The compound (XVIII) is an isomerization product of (XVII).[11]

In a Grignard reaction and a metal hydride (weak nucleophile, *e.g.*, AlH_3 and AlH_2Cl) reduction of epoxides, it is well known that rearrangement to a carbonyl intermediate followed by nucleophilic addition competes with direct nucleophilic ring-opening of epoxide.[12,13] The result presented in this chapter is the first example of a Friedel-Crafts type reaction in which the rearrangement to

Table 2. Products of the reaction of various epoxides with anisole (AnH) by aluminum chloride in nitromethane[a)]

	Epoxide	Product	Isomer distribution in bis(methoxyphenyl) derivatives[b)]		
			o,o-	*o,p-*	*p,p-*
1	MeCH—CH_2 (O)	$EtCH(An)_2$ (**1**, 28%)	1.4	24.8	73.8
2	EtCH—CH_2 (O)	$PrCH(An)_2$ (**9**, 33%)	1.7	24.8	73.5
3	*n*-BuCH—CH_2 (O)[d)]	$CH_3(CH_2)_4CH(An)_2$ (**10**, 32%)	2.5	23.3	74.2
4	$ClCH_2CH_2$—CH_2 (O)	None			
5	PhCH—CH_2 (O)	$PhCH_2CH(An)_2$ (**11**, 46%)	2.6	25.0	72.4
6	Ph, Me C—CH_2 (O)[e)]	Ph, Me CHCH$(An)_2$ (**12**, 76%)	0.7	22.2	77.1
7	Et_2C—CH_2 (O)[f)]	$Et_2CHCH(An)_2$ (**13**, 40%)	2.3	18.2	79.5
8	PhCH—CHPh (O)[g)]	$Ph_2CHCH(An)_2$ (**14**, 56%)[c)]	2.2	24.7	73.1
		$PhCH_2CH$<Ph, An (**15**, 11%)			
		Ph, An C=CHAn (**16**, 10%)			
9		 $-CH(An)_2$ (**17**, 17%)	0.7	23.0	76.3
		 CH_2An, An (**18**, 8%)			
10	 Me[h)]	 $CH(An)_2$, Me (**19**, 5%)	0.9	22.6	76.5

a) Reactions were conducted with anisole (100 mmol) and $AlCl_3$ (40 mmol) in nitromethane (40 ml), and the epoxide (20 mmol) in nitromethane (20 ml) at 0—2 °C, the mixtures were homogeneous. Isolated yields given in parentheses were calculated on the basis of the epoxides used. b) Calcd from GLPC. c) The possibility of contamination of 1,2-bis(methoxyphenyl)-1,2-diphenylethane cannot be excluded. d) bp 117—118 °C (lit,[15a)] bp 116—119 °C). e) bp 98—100 °C/33 mmHg (lit,[15b)] bp 71 °C/10 mmHg). f) bp 105—106 °C (lit,[15c)] bp 105—107 °C). g) mp 68—69 °C (lit,[15d)] mp 68.5—69 °C). h) bp 72—74 °C/105 mmHg (lit,[15e)] bp 137—138 °C).

aldehyde followed by condensation has been shown to be the main reaction path.[14]

3 Experimental

NMR and IR spectra were recorded on a JEOL PMX-60 or a Varian HR-220, and a Hitachi EPI-G2 spectrometers, respectively.

Propylene oxide, 1,2-epoxybutane, and styrene oxide were dried over sodium carbonate and distilled before use. Commercial cyclohexene oxide was used without further purification. Other epoxides were prepared by *m*-chloroperbenzoic acid oxidation of the corresponding olefins.[15] Commercial aluminum chloride (GR grade) was used without further purification. Anosole and nitromethane were dried over sodium hydroxide and phosphorous pentoxide respectively, and distilled before use.

Reaction of Propylene Oxide with Excess Anisole in 1,2-Dichloroethane in the Presence of Aluminum Chloride. To a stirred and cooled (ice bath) solution of 108 g (1.0 mol) of anisole and 14 g (0.11 mol) of aluminum chloride in 200 ml of 1,2-dichloroethane, a mixture of propylene oxide (5.8 g, 0.1 mol) and anisole (54 g, 0.5 mol) was added dropwise during the course of 1.5 h. After 2.0 h, reaction was quenched with 300 ml of water and the organic layer was washed with 100 ml of water three times. The combined water layers were extracted with 200 ml of ether three times. The combined organic layers were dried over magnesium sulfate.

After removal of the solvents, the product was distilled under reduced pressure: 1st fraction, 70-82 °C / 15 mmHg, (III),(IV), and recovered anisole; 2nd fraction, 0.2 g, 42 °C / 5.7 mmHg, phenol; 3rd fraction, 0.7 g, 98 °C / 5.0 mmHg, (VI); 4th fraction, 107-111 °C / 4.8 mmHg, (V); 5th fraction, 6.0 g, 140-169 °C / 3.2 mmHg, (I). GLPC analysis showed that the 4th fraction contained 57% and 43% of *o*- and *p*-isomers of (V) respectively together with small amounts of (I) and (VI). To confirm the structure of (V), a paramagnetic shift experiment in the NMR spectra was carried out using tris(2,2-dimethyl-6,6,7,7,8,8,8-pentafluoro-3,5-octanedionato)europium(III). Results are shown in Fig. 1.

Reaction of Methoxyphenylpropanols with Anisole in the Presence of Aluminum Chloride. In an ice bath, (V) (10 mmol, 70% of *o*- and 30% of *p*-isomer) was treated with anisole (11 g) in the presence of aluminum chloride (20 mmol) for 2 h. After the usual treatments, the reaction mixure was distilled. The yield of a mixture of (I) and (II) (146-172 °C / 3.3 mmHg) was 53%. NMR analysis showed that the product contained 20% of (I) and 80% of (II).

Reaction of Propionaldehyde with Anisole in the Presence of Aluminum Chloride. Propionaldehyde (0.1 mol) was added to anisole (0.2 mol) in 1,2-dichloroethane (300 ml) in the presence of aluminum chloride (0.1 mol) at room temperature for 3.5 h. After the usual work up, 31.7 g of a residual product was obtained. GLPC analysis showed that (I) was

formed as a main product, along with many others. Products were separated by column chromatography on silica gel using 30% benzene-hexane.

Reaction of Propylene Oxide with Anisole in the Presence of Aluminum Chloride—— Effects of Reaction Conditions. The following example shows a typical experimental procedure. To a solution of anisole (4.33 g) and aluminum chloride (2.7 g) in 1,2-dichloroethane (40 ml) was added 1.33 g of propylene oxide over a period of 2 h at ice-bath temperature. The reaction mixture was stirred at that temperature for an additional 1.5 h. Then the reaction was quenched with a mixture of ice water (50 ml) and concd hydrochloric acid (5 ml). The organic layer was washed with 20 ml of water. The combined water layers were extracted twice with 50 ml of ether and twice with 30 ml. The combined organic layers were dried over magnesium sulfate and distilled to remove the solvent. GLPC analysis of the residual products using dibutyl phthalate as an internal standard showed 785 mg of (I) was formed in this reaction.

Reaction of 1,2-Epoxybutane with Anisole in the Presence of Aluminum Chloride in Nitromethane Solvent. To a mixture of anisole (100 mmol), aluminum chloride (40 mmol), and nitromethane (40 ml) was added a mixture of 1,2-epoxybutane (20 mmol) and nitromethane (20 ml) during the course of 45 min in an ice bath. After an additional 2.5 h, the reaction was quenched as mentioned above. After removal of the

solvents, the residual product was purified by chromatography with silica gel, using benzene as an elutant. Distillation of the crude product by a ball-oven apparatus yielded 1,79 g (33.0%) of (IX), bp 169-172 °C / 2.5 mmHg. Isomers of the products could be separated by further chromatography using benzene-hexane (1:10) as an elutant. Elemental analyses and NMR spectra are shown in Table 3. The mass spectrum of di-*p*-isomer of (IX) was: m/e (rel. intensity); 270 (M^+, 18), 227 (100), 121 (45).

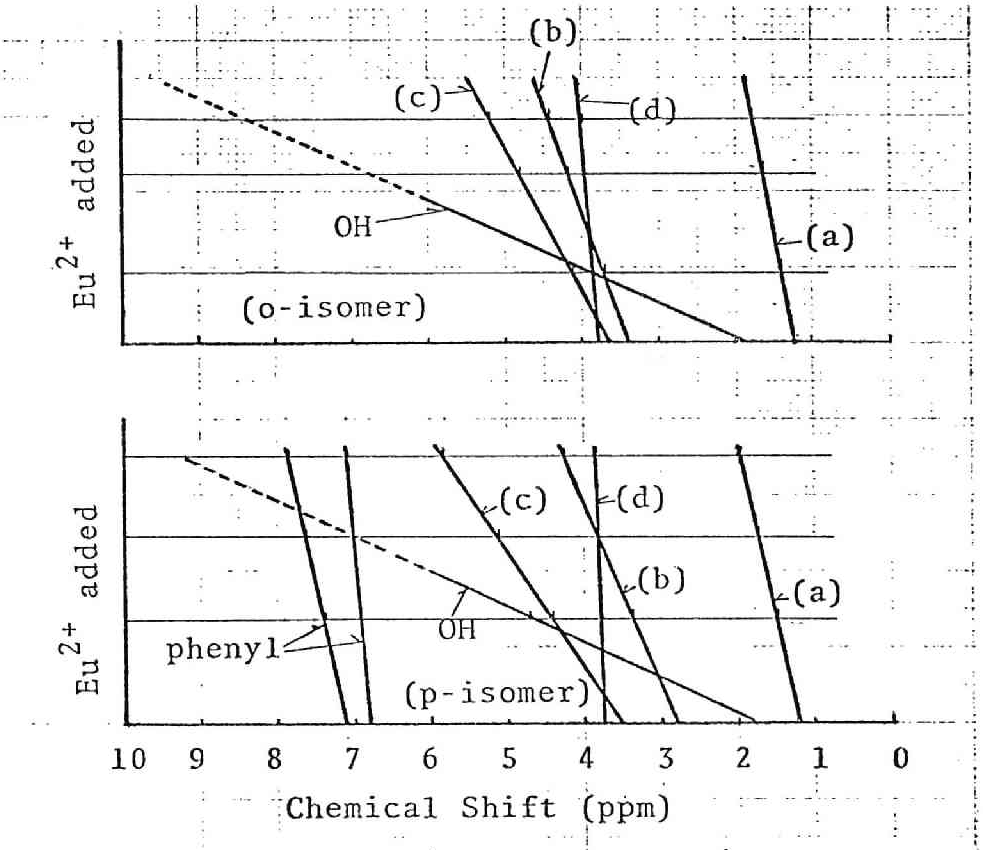


FIGURE 1. PARAMAGNETIC SHIFT EXPERIMENT

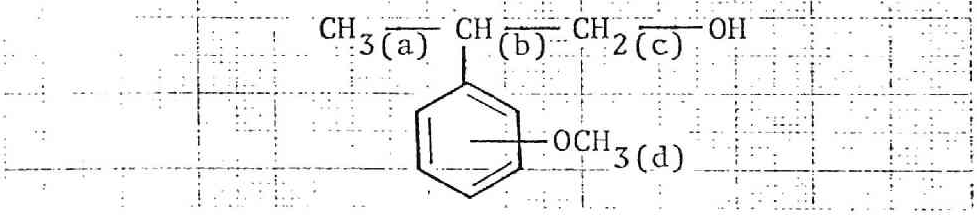


Table 3. Analytical data

Compound		Bp or mp °C	Formula	Calcd		Found		NMR (δ)		
				C%	H%	C%	H%	CH_3O-		-CH(An)$_2$
1	-*p*,*p*[a]	bp 166—172/ 3.2 mmHg	$C_{17}H_{20}O_2$	79.65	7.86	79.90	8.13	3.73		3.72
1	-*o*,*p*[a]					79.86	7.60	3.76	3.74	4.24
2	-*p*,*p*	mp 66.5—68	$C_{17}H_{20}O_2$	79.65	7.86	79.35	7.91	3.74	3.75	
2	-*o*,*p*					79.51	8.03			
2	-*o*,*o*					79.66	8.04			
8	-*p*,*p*	mp 93—95[b]	$C_{17}H_{18}O_2$	80.26	7.13	79.98	7.39	3.77	3.82	
9	-*p*,*p*[a]		$C_{18}H_{22}O_2$	79.96	8.20	79.84	8.10	3.7[2]		3.7[7]
9	-*o*,*p*[a]					80.19	8.01	3.7[4]	3.7[5]	4.3[7]
10	mixt		$C_{20}H_{26}O_2$	80.49	8.78	80.19	8.75			3.8 (*p*,*p*-), 4.3[5] (*o*,*p*-)
11	-*p*,*p*	mp 97.5—98.5[c]	$C_{22}H_{22}O_2$	82.98	6.96	82.71	7.05	3.7[2]		3.2[7] (*o*,*p*-; 4.7[0])
12	-*p*,*p*		$C_{23}H_{24}O_2$	83.10	7.28	82.79	7.49	3.6[8]	3.4[5]	3.9[3]
12	-*o*,*p*							3.7[0]	3.4[6]	4.6[0]
13	mixt		$C_{20}H_{20}O_2$	80.49	8.78	80.52	8.87			3.5[8] (*p*,*p*-), 4.2[2] (*o*,*p*-)
14	mixt	mp 196—199								4.6[5] (*p*,*p*-), 4.7[7] (*o*,*p*-)
15	-*p*	mp 84—85[d]	$C_{21}H_{20}O$	87.46	6.99	87.52	7.06	3.6[8]		(3.2[8], d, 1; 4.1[7], t, 2, J=8 Hz)
15	-*o*					87.34	6.78	3.5[8]		(3.2[8], d, 1; 4.7[2], t, 2, J=8 Hz)
16	-*p*,*p*[e]	mp 89—91[f]	$C_{22}H_{20}O_2$	83.51	6.37	83.49	6.65			
17	-*p*,*p*		$C_{20}H_{24}O_2$	81.04	8.16	81.27	8.12	3.7[5]		3.5[0]
17	-*o*,*p*					81.25	8.46	3.7[5]	3.7[6]	4.1[0]
18	-*p*,*p*		$C_{20}H_{24}O_2$	81.04	8.16	81.15	7.86	3.7[0]		(2.7[1], s, 2, -CH_2An)

a) These products were mentioned by V. A. Topchii, S. V. Zavgorodnii, A. I. Bazaeva, and Ya. I. Yashin, *Izv. Vyssh. Uchebn. Zavend., Khim. Khim. Tekhnol.*, **13**, 1755 (1970), from *Chem. Abstr.*, **75**, 76327f (1971). b) Lit, mp 105 °C, F. v. Wessely, E. Kerschbaum, and A. Kleedorfer, *Monatsh.* **73**, 127 (1940), from *Chem. Abstr.*, **35**, 1781[2] (1941). c) Lit, mp 96—97 °C, K. Sisido, K. Okano, and H. Nozaki, *J. Am. Chem. Soc.*, **77**, 4604 (1955). d) Lit, mp 84—85 °C (*p*-isomer) mp 62—64 °C (*o*-isomer), G. Capozzi, G. Melloni, and G. Modena, *J. Chem. Soc., C*, 1970, 2621. e) This product may be a mixture of *cis* and *trans* isomers. f) Lit, mp 93—94 °C for *cis* isomer, mp 104.5—105.5 °C for *trans* isomer, Z. Rappoport and Y. Apeloig, *J. Am. Chem. Soc.*, **91**, 6743 (1969).

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8) For detailed discussion, see Chapter IV of this thesis.

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11) The reaction of epoxycyclohexane with excess anisole without solvent yielded (XVII) and *trans*-2-(*o*- and *p*-methoxyphenyl)cyclohexanols, and (XVIII) was not detected.

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14) Recently Sekiguchi *et al*. proposed a similar reaction sequence for the reaction of styrene oxide with benzene in the presence on aluminum chloride. K. Kimura, Y. Hayami, K. Matsui, and S. Sekiguchi, Abstr. No. 2D18, 32th National Meeting of the Chemical Society of Japan, Tokyo, April 1975.

15) a) D. J. Pasto and C. C. Cumbo, *J. Org. Chem.*, 30, 1271 (1965); b) R. E. Parker and B. W. Rockett, *J. Chem. Soc.,(B)*, 1966, 681; c) B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*,93, 1693 (1971); d) D. E. Bissing and A. J. Speziale, *ibid.*, 87, 2683 (1965); e) D. K. Murphy, R. L. Alumbaugh, and B. Rickborn, *ibid.*, 91, 2649 (1969).

CHAPTER IV Intermolrcular Hydride Transfer Reaction Accompanied by Freidel-Crafts Reaction[1)]

Friedel-Crafts reaction of benzene with 1,2-dihalogenated propanes, allyl alcohol, 2-phenyl 1-propanol, and the related compounds gave a mixture composed of 1,1- and 1,2-diphenylpropanes, propyl benzene, and 1,1-diphenylpropene. The latter two are hydrogenation-dehydrogenation reaction products which are concluded to be formed by intermolecular hydride transfer from 1,1-diphenylpropane to the intermediate, 1-phenyl-2-propyl or 1-phenyl 1-propyl cation. In the case of allylbenzene, the hydride transfer reaction was not observed except at a high reaction temperature. A mechanism which can explain all of the results reported so far is proposed.

1 Introduction

It is well known that Friedel-Crafts reactions sometimes accompany undesired reactions to yield complex product mixtures.[2)] One of the side-reactions is oxidation-reduction reaction, and the reduced products have been widely recognized as hydrocraking products.[3)] However, only few oxidized products were confirmed, one of which is 9,10-dialkylanthracene formed in Friedel-Crafts reaction of benzene

with allyl chloride or vinyl chloride,[4] and this causes a great difficulty in understanding of the reaction mechanism.

During the course of a study on the Friedel-Crafts alkylation with epoxides (chapter III), it was found that 1,2-dihalopropanes gave propylbenzene (I, a reduced product) and 1,1-diphenylpropene (II, a oxidazed product) together with the ordinary products of 1,2-diphenylpropane (III) and 1,1-diphenylpropane (IV). This reaction system is particularly worthy to note, because it affords the simplest oxidized product.[5] Therefore, many alkylating agents which are expected to give (III) and (IV) were examined. This chapter reports the experimental results and discusses the reaction mechanism.

2 Results and Discussion

Table 1 shows the results of Friedel-Crafts reaction with various kinds of alkylating agents. The results are summerized as follows: (1) Although the earlier papers of literature reported that these reaction system afforded (III),[6] the formation of (IV) was always observed as a minor product.[7] (2) Under drastic conditions, however, (IV) was not detected. (3) The reaction systems afforded (I) as a reduced product, but cumene was not detected, whose formation was reported erroneously by Ransley in the reaction of 1,2-dichloropropane.[8] (4) In all the reaction systems, (II) was formed as a oxidized product.

Table 1 Friedel-Crafts Reaction[a)]

Alkylating agent	Temp[b)] °C	Mol[c)] ratio	Yield[d)] (%) (I)	(II)	(III)+(IV)	Distribution (%) (III)	(IV)
$CH_3\underset{Cl}{\underset{\vert}{CH}}-\underset{Cl}{\underset{\vert}{CH_2}}$	19	I	13.0	3.2	57.0	84	16
$CH_3\underset{Cl}{\underset{\vert}{CH}}-\underset{Cl}{\underset{\vert}{CH_2}}$	63	I	22.0	2.0	24.2	100	0
$CH_3\underset{Br}{\underset{\vert}{CH}}-\underset{Br}{\underset{\vert}{CH_2}}$	25	II	11.1	5.8	33.2	83	17
$CH_2=CHCH_2Cl$	10	II	(4.7)	(0.0)	(30.3)	66	34
$CH_2=CHCH_2Br$	10	II	(7.0)	(tr)	(36.8)	88	12
$CH_3\underset{Cl}{\underset{\vert}{CH}}-CH_2Ph$	10	II	9.8	4.8	62.8	98	2
$CH_3\underset{OH}{\underset{\vert}{CH}}-CH_2Ph$	40	III	9.0	3.1	66.5	93	7
$CH_3\underset{OAc}{\underset{\vert}{CH}}-CH_2Ph$	22	III	9.2	2.8	43.8	—	—
$CH_3\underset{OAc}{\underset{\vert}{CH}}-CH_2Ph$	50	III	11.3	tr	53.2	91	9
$CH_2=CHCH_2Ph$	25	II	0.0	0.0	(35.4)	73	26
$CH_3\underset{Ph}{\underset{\vert}{CH}}-CH_2OH$	40	III	9.7	2.1	67.9	93	7
$CH_3\underset{Ph}{\underset{\vert}{CH}}-CH_2OAc$	22	III	15.5	5.6	51.6	—	—
$CH_3\underset{Ph}{\underset{\vert}{CH}}-CH_2OAc$	50	III	—	(0.4)	(29.0)	93	7

a) Alkylating agents were added to a mixture of benzene and $AlCl_3$ over a period of 10 min, and then the mixture was stirred for an additional 1 h. b). ±2 °C. c) Alkylating agent/$AlCl_3$/benzene are as follows: I,1:0.4:40; II, 1:0.4:10; III, 1:1.2:10. d) Calcd from GC (isolated yield are given in parentheses).

9,10-Diethylanthracene was not detected except in the case of allyl halides.[4] (5) The yields of (I) were always higher than those of (II). (6) In the reaction of allylbenzene (V), oxidation-reduction reaction was not observed.

As it is exceptional that Friedel-Crafts reaction of (V) does not accompany oxidation-reduction reaction, the reaction of (V) was explored further. The results are given in Table 2, and are summerized as follows: (7) The relative yield of (III) vs. that of (IV) appeared to increase at higher reaction temperatures. (8) On the contrary, at further higher temperature, the relative yield of (III) decreased, and (I) was formed which is not observed at lower temperatures. (9) The relative yield of (IV) increased with an increase of solvent polarities.

The results can be explained by the following reaction paths (scheme 1). Initial alkylation products, 1-halo-2-phenylpropane and/or 2-halo-1-phenylpropane are formed from 1,2-dihalopropanes and allyl halides (path a). As neighboring phenyl group in the initial products assists the ionization of the halogen-carbon bond in the products (path b),[9] subsequent alkylation proceeds faster than initial alkylation, and the initial products cannot be obtained in the experiments of 1,2-dihalopropanes and allyl halides. When two different substituents are attached to propane, one of which is readily and the other is less ionizable, the latter remains in the initial alkylation products when

Table 2 Friedel-Crafts Reaction of Allylbenzene.[a)]

Reaction Temp °C	Solvent	Mol ratio[b)]	Yield[c)]	Distribution (III)	Distribution (IV)
10		I	38.3	76	24
20		II	42.3	82	18
25		I	35.4	73	27
40		I	35.9[d)]	85	15
40		II	49.9	64	36
10	$ClCH_2CH_2Cl$	III	44.3	91	9
10	C_6H_5Cl	III	42.9	62	38
10	CH_3NO_2	III	10.5	40	60
-15	CH_3NO_2	III	10.1	89	11

a) See foot notes of Table 1. b) Alkylating agent/$AlCl_3$/benzene are as follows: I, 1:0.4:10; II, 1:0.4:100; III, 1:0.4:4. In the case of III, 40 ml of solvents were used to 25 mmol of alkylating agent.

c) Isolated yields of diphenylpropanes.

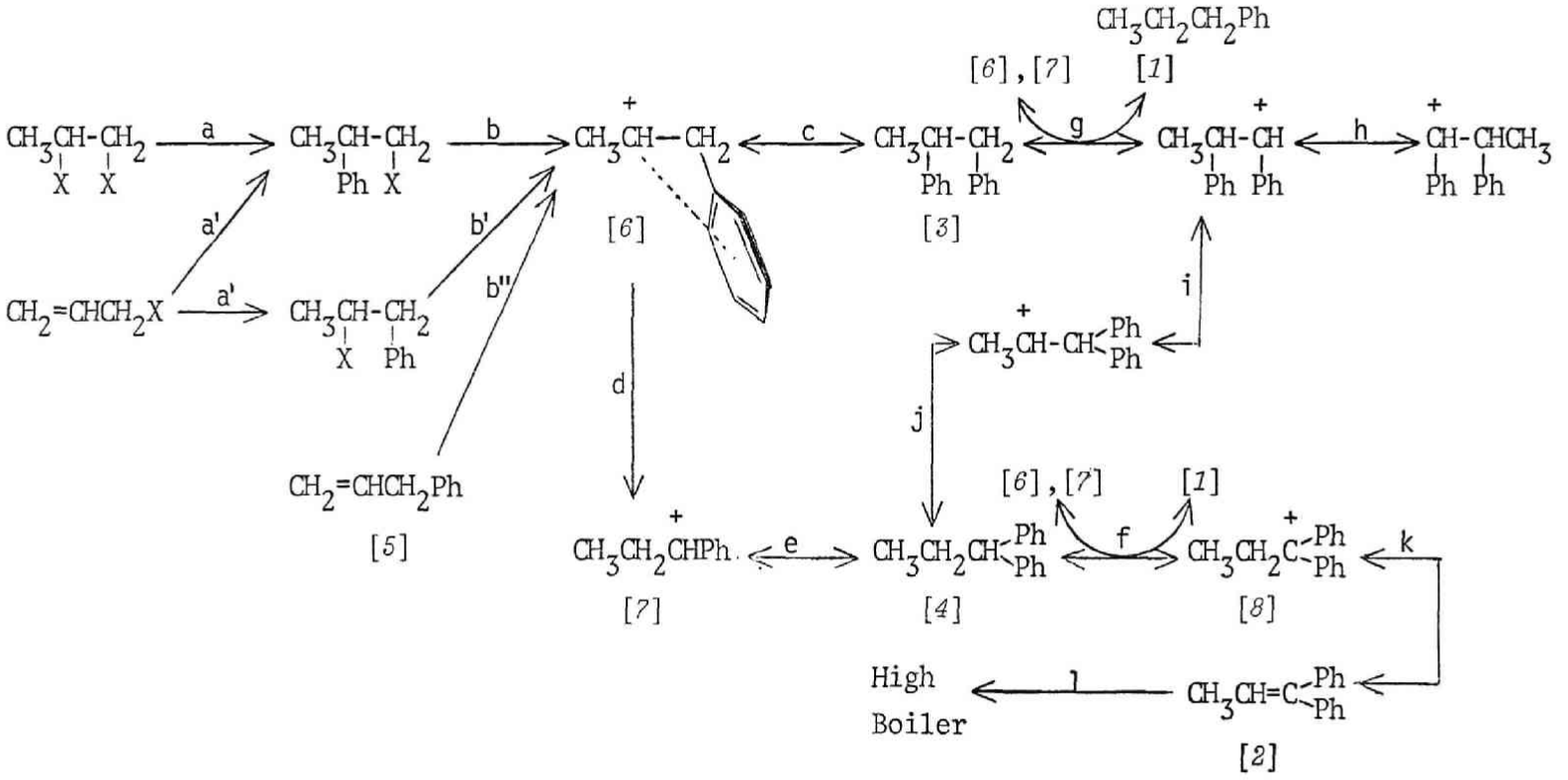
d) Propylbenzene was isolated in a 9.0% yield.

they can be isolated.[5b,10]

Masuda *et al.* examined the Friedel-Crafts alkylation with optically active 2-chloro-1-phenylpropane, which yielded (III) with retained configuration, and assumed an intermediate ion (VI) which they correctly depicted as shown in shcheme 1.[11] The ion (VI) is not a nonclassical phenonium ion but an ion in which π electrons of phenyl group interact with the vacant p-orbital of the carbon atom. This type of ion has been discussed by means of *ab intio* caluculation[12] and super acid solution technique.[13]

As 1-phenyl 1-propyl cation (VII) is more stable than (VI), the cation (VI) rearranges to (VII) readily at higher temperatures (results 1 and 7) and in polar solvents in which cations have longer life times (result 9). Paths c and e are actual alkylating stages and proceed faster than ionizing atage (path b).

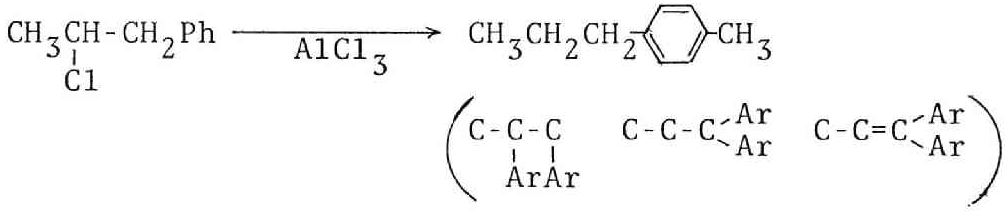
It is most reasonable to consider that oxidation-reduction reaction is caused by the intermolecular hydride transfer from (IV) to cation (VI) or (VII) (path f). This reaction path leads (IV) to resonance stabilized 1,1 diphenyl 1-propylcation (VIII), from which (II) is formed by loss of proton (path k), and (VI) or (VII) to reduced (I) (results 3 and 4). As (II) is converted into high boiling tarry matter *via* futher alkylation or polymerization (path l), the yields of (I) are always larger than those of (II) (result 5). Under drastic conditions, (IV) is



Scheme 1

converted into high boiler *via* paths f, k, and l, and no or reduced amounts of (IV) are observed (results 2 and 8), which seems to be a reason why earlier papers reported the formation of only (I) and (III).[6] Ransley reported that the relative amount of (IV) vs. that of (III) decreased after prolonged reaction times,[8] which can be explained along the same line.

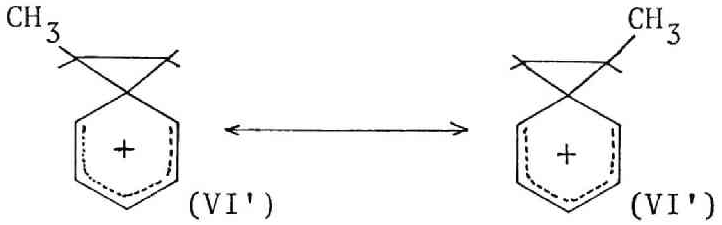
To obtain further evidence to the reaction mechanism of hydride transfer, the reaction of toluene with 2-chloro-1 phenylpropane was examined. Though no imformation could be obtained concerning the diaryl products because of complex positional isomers on phenyl ring, only 1-methyl-4-propyl-benzene is obtained as a reduced product without any contamination of propylbenzene.



This fact indicates that alkylation (paths c and e) proceeds faster to form (III) and (IV) and is followed by slow dealkylation (reverse paths c and e) and hydride transfer reaction. This consideration agrees with Heesing's results that (II) is formed in the latter stage of the reaction.[5a]

Recently Heesing *et al.* reported the results of alkylation with allyl alcohol.[5a] They explored the reaction

with the isotopically labeled starting materials and found that heavy atoms in C_1 or C_2 position of allylalcohol are completely scrumbled in C_1 and C_2 positions of the products (I), (III), and (II). They atributed this fact to the automerization (isotopic reaarengement) in phenonium ion (VI'). However, their conclusion can not explain the



results reported by Masuda *et al.*,[11] because only a slight decrease of optical purity should take place in cation (VI) on the basis of Masuda's results, and because the proposed path by Heesing *et al.* should result in complete racemization by methyl group rearrangement.

Heesing *et al.* ignored the secondary rearrangement shown by paths f-i in scheme 1,[14] by the results of their controll experiment in which the reaction of the labeled (III) at C_2 position by ^{13}C with aluminum chloride resulted in no scrumbling. However, it is well known that isomerization of alkylbenzenes takes place readily in the presence of alkyl halide as a cation precursor.[15] It must be noted that in their expriment of alkylation with allyl alcohol, the starting material (allyl alcohol), the primary product (2-phenylpropanol), and product (II), which can act

as cation precursors, exist together with products (III) and (IV). Therefore, the conditions of their contoroll experiment differ with those of alkylation reaction, and the secondary isomerization processes shown by paths f-i in scheme 1 are undeniable.[16]

Finally, it is interesting that Friedel-Crafts reaction of benzene with (V) does not accompany intermolecular hydride transfer reaction. At the present time, it seems to be most probable to consider that water and hydrogen halides, which are released in the alkylation from all the alkylating agents except allylbenzene, act as co-catalysts for intermolecular hydride transfer reaction.

3 Experimental

The reaction conditions of Friedel-Crafts alkylation are shown in the foot notes in Tables 1 and 2. After the usual work up of the reaction mixture, the yields of the products were determined by means of GLCP (Hitachi 163, PEG 20M), using *p*-methylanisole as a internal standard.[17] The isomer distributions in diphenylpropanes, (III) and (IV), were determined from the intensity integral of the methyl protons on NMR spectra (JEOL PMX-60 spectrometer) after isolation of the products.

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6) See for example, R. C. Huston and D. D. Sager, *J. Am. Chem. Soc.*, 48, 1955 (1926).

7) For the reports which described the formation of (IV); Refs. 9 and 11, and Y. Butsugan, K. Kawase, K. Saheki M. Muto, and T. Bito, *Nippon Kagaku Kaishi*, 1973, 2338.

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15) Refs. 9 and 14, and references cited therein.

16) The duterium distribution in the products reported by Heesing *et al.* can be explained completely by scheme 1.

17) As the retention times of (III) and (IV) are same on GLPC analysis, the sum of the yields of (III) and (IV) was determined. The correction factors for the two products were assumed to be equal.

PART II

SOLVOLYSIS OF *trans*-2,3-DIPHENYLOXIRANE. CO-SOLVENT EFFECTS ON STEREOCHEMISTRY OF THE REACTION

CHAPTER V Medium Effects on Stereochemistry of Acid-Catalyzed Ethanolysis of *trans*-2,3-Diphenyl oxirane

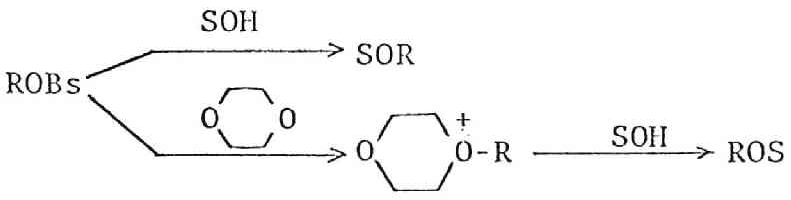
The acid catalyzed ethanolysis of *trans*-2,3-diphenyloxirane was examined in a wide variety of binary ethanolic solvent systems. The reaction proceeded with 26% retention and 74% inversion of configuration in pure ethanol at 50 °C. When ethanol was diluted with hexane or benzene, the stereochemical outcome of the ethanolysis was virtually unchanged. The addition of acetonitrile, nitromethane, or sulforane to the ethanolic solution resulted in increased degrees of retention. On the contrary, increased ratios of inverted product were obtained in binary ethanolic mixtures containing DMSO, DMF, or HMPA. Steric course of the ethanolysis could be controlled from 85% retention-15% inversion (CH_3NO_2: ethanol = 20:2 by volume) to 10% retention-90% inversion (HMPA:ethanol = 10:12) by the choice of co-solvent. The results are discussed in terms of solvation shell concept.

1 Introduction

Needless to say, reaction media have enormous effects

on organic reactions, and many papers have been published about the solvent effects on reaction kinetics. Since the physical properties can be varied continuously by changing the composition of the solvents, binary solvent systems are particularly interesting, and a number of papers discussed the reaction kinetics in binary solvent mixtures. The paper reported by Arnett and his co-workers seems to be remarkable since they have shown that the rates of solvolysis of *tert*-butyl chloride in aqueous mixture are determined by changes in the stability of the *ground state* and not of the transition state.[1)]

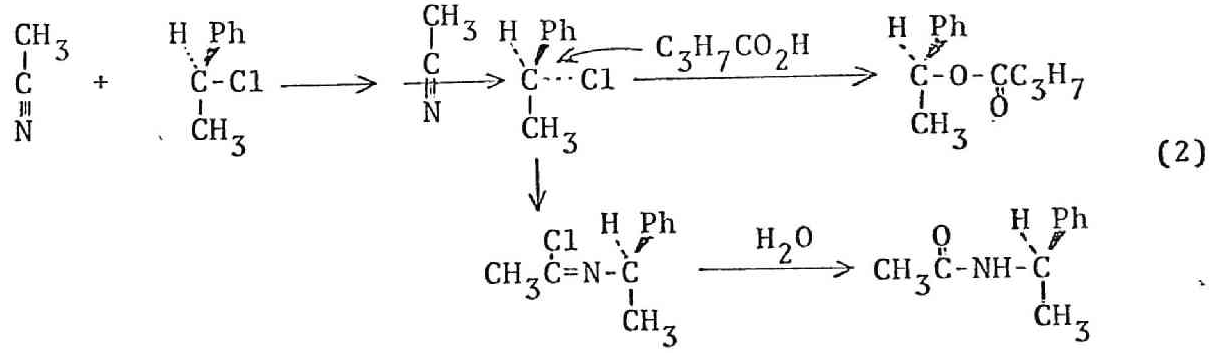
Although the effects of the composition of the binary solvent mixture on the steric course of reaction seem to be also interesting, only a few papers dealt with this problem. The results of the solvolysis of optically active 2-octyl *p*-bromobenzenesulfonate by Weiner and Sneen[2)] are the most famous and have been quoted in many texbooks. The reaction in 75% aqueous dioxane gave inverted 2-octanol in 77% optical purity, whereas solvolysis of this compound in pure water resulted in 100% inversion of configuration. They explained the results by assuming an intermediate, an oxonium ion formed by an S_N2 attack by dioxane (Eq. 1).



(1)

A quite similar mechanism was proposed by Streitwieser for the solvolysis of optically active 1-butyl-1-*d* *p*-nitrobenzenesulfonate in the mixtures of dibutyl ether and acetic acid.[3)]

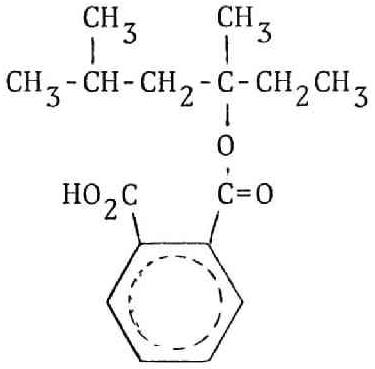
Okamoto and his co-workers found that the butyrolysis of optically active 1-phenylethyl chloride in pure butanoic acid gave 1-phenylethyl butanoate with 3.5% net inversion, and that the reaction proceeded faster in a binary solvent system of butanoic acid and acetonitrile than in pure butanoic acid to yield the product with 2.9% net retention, and a small amount of *N*-1-phenylethyl acetamide was also isolated with net (3.2%) inversion.[4)] They explained the results by the following reaction scheme, which includes a nucleophilic solvation of an ion-pair intermediate from the side opposite to that of the leaving group, *i.e.* a back-side shielding mechanism.



(2)

The largest variation in the steric course of solvolytic reactions with the variation of the composition of binary solvent mixture was found in the acid-promoted methanolysis

of 3,5-dimethyl-3-hexyl hydrogen phthalate.[5] In pure methanol, steric course of the reaction was 60% net inversion, whereas the result was 100% recemization in a mixture of 20% methanol and 80% nitromethane. Unfortunately, complete discussion and experimental details are not yet published.



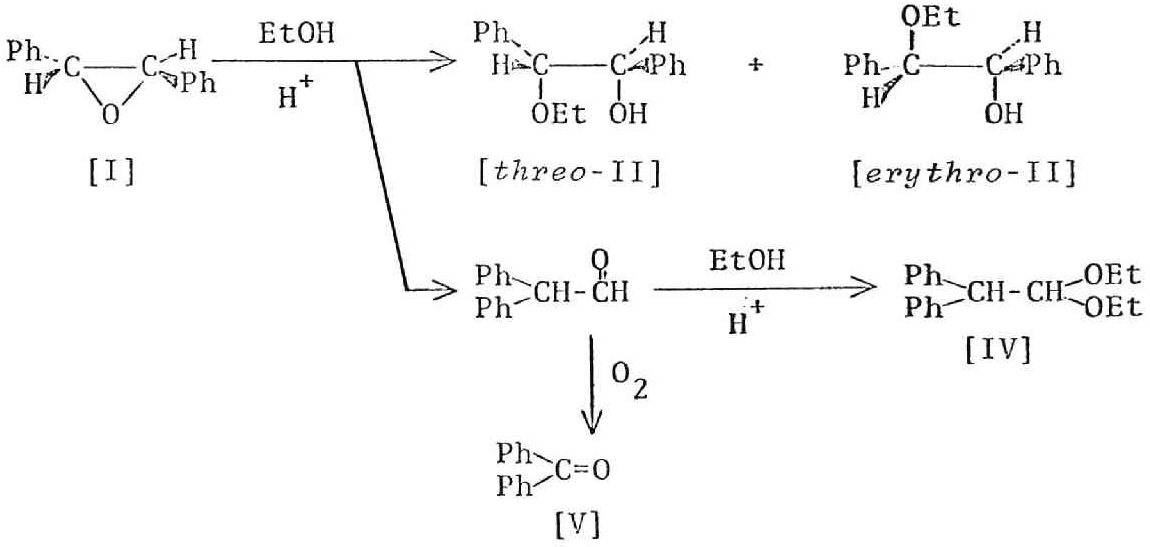
On the steric course of epoxide ring-opening, Italian workers proposed a back-side shielding mechanism for the trichloroacetolysis of aryl-substituted epoxycyclohexanes,[6] and Ito reported that the dielectric constant of medium is an important factor affecting the steric course of the hydrolysis of 2,3-diphenyloxirane.[7] However, these workers did not explore the effects of the composition of binary solvent mixtures. Therefore, aryloxiranes are interesting compounds for stereochemical investigations on the medium effects in binary solvent systems.

This chapter reports the experimental results of the acid-catalyzed ethanolysis of *trans*-2,3-diphenyloxirane [I] in binary ethanolic mixtures containing various kinds of co-solvents (solvents added to ethanol), and discusses the relationship between the steric course of the reaction and the nature of solvation in binary solvent mixtures.

2 Results

Acid-catalyzed ethanolysis of [I] in pure ethanol gave *threo*- and *erythro*-2-ethoxy-1,2-diphenylethanols [*threo*- and *erythro*-II], diphenylacetaldehyde [III], and 1,1-diethoxy-2,2-diphenylethane [IV] (the diethyl acetal of [III]) as shown in scheme 1, and total yields of the four compounds were more than 90% by GC analysis and more than 80% after isolation.

As the autoxidation catalyzed by potassium carbonate[8] which was added to neutralize the catalyst acid converted [III] completely into benzophenone [V] (see experimental section), the yields of [V] can be presumed to be those of [III]. To check the possibility of the formation of [V] during the ethanolysis, the reaction mixture was subjected to GC analysis directly without potassium carbonate treatment. The yield of [V] was less than 0.5%, which would be attributed to the oxidation of [III] under the ethanolysis conditions.



Scheme 1

As the author was concerned mainly with the steric course of ethanolysis of [I], detailed processes of the oxidation was not examined.

Table 1 shows the effects of concentrations of acid and [I] on the product distribution of ethanolysis in pure ethanol at 50 °C. Obviously, the ratio of the two ethanolysis products, [*threo*- and *erythro*-II], was not affected within an experimental error, whereas the reaction rate increased with the increase of acid concentration. This fact shows that both of the stereoisomeric [II]s are formed through a common intermediate, *i.e.* conjugate acid of [I], [I-H^+]. In a high acid-concentration condition, 1-ethoxy-2,2-diphenylethene [VI] was observed in the latter stage of the reaction, and seemed to be formed by elimination of ethanol from [IV].

Table 2 shows the variation of the yield of the products with the variation of the composition of ethanol-acetonitrile system at 70 °C. With an increasing percentage of acetonitrile, the reaction rate decreased and the proportion of the retained product [*threo*-II] increased, though the yields of the rearranged products, [IV] and [V], also increased. The formation of the other products than those listed in Table 2 was only inconsiderable in amount except in the case of the solvent system composed of 91% acetonitrile by volume. As many unexpected products were detected on GC analysis in the experiment of 91% acetonitrile, isolation of the procucts

TABLE 1. ETHANOLYSIS OF [I] IN PURE ETHANOL AT 50°C

[I]	$[H^+]$ a)	Total yield	Product distribution			
			Rearr. b)	[*threo*-II]	[*erythro*-II]	Ret c)
mmol l^{-1}	mmol l^{-1}	%	%	%	%	%
9.1	0.91	92	10	23	67	26
23.2	0.91	93	11	23	66	26
46.4	0.91	99	12	23	65	26
92.7	0.91	93	11	23	66	26
46.4	7.85	89	12	23	65	26
46.4	0.78	92	12	23	65	26

a) H_2SO_4 was used. b) [IV] + [V]. c) ([*threo*-II] / [II]) × 100

TABLE 2. ETHANOLYSIS OF [I] IN ETHANOL-CH_3CN AT 70 °C

CH_3CN Vol %	Yield (%)					Ret.[a] %
	[I]	[IV]	[V]	[*threo*-II]	[*erythro*-II]	
0	0	15	tr	25	54	31
9	0	19	tr	28	48	37
23	0	21	3	32	41	44
36	0	18	10	35	35	50
46	0	18	12	36	32	53
68	5	10	23	34	18	65
91[b]	33	4	32	21	4	85

a) See foot note of Table 1. b) Several other products were detected, see text.

TABLE 3. ETHANOLYSIS OF [I] IN ETHANOL-CH_3CN AT 50 °C

CH_3CN Vol %	Yield (%)					Ret.[a] %
	[I]	[IV]	[V]	[*threo*-II]	[*erythro*-II]	
0	0	11	1	22	63	26
9	0	12	2	25	55	31
23	0	12	7	30	48	38
36	7	6	14	32	40	44
46	12	4	14	31	34	48
68	38	2	16	26	17	60
91[b]	73	1	16	14	3	83

a) See foot note of Table 1. b) Trace amounts of 1,2-diphenylethanol [X] and benzyl phenyl ketone [VII] were observed.

was carried out by column chromatography. The isolated products were as follows: [*threo*-II], 28%; [*erythro*-II], 8%; [V], 21%; [III], trace; [IV], 13%; [VI], 7%; benzyl phenyl ketone [VII], 1%; 2-hydroxy-1,2-diphenylethanone [VIII], 4%; diphenylethanedione [IX], trace; 1,2-diphenylethanol [X], 2%; 2,2-diphenylethanol [XI], 3%.

The compound [VII] is another rearranged product of [I], and a trace of [VII] was always observed on GC analysis in all experiments throughout this chapter. The last four are the redox-reaction products.

Table 3 shows the results of ethanolysis at 50 °C in ethanol-acetonitrile system. Quite similar results to those in Table 2 are observed, but the proportion of the retained product [*threo*-II] at 70 °C was always higher, as compared with the results of the same solvent composition at 50 °C.

Table 4 shows the variation of the product distribution with the change of reaction time. As shown in Table 4, [IV] seems to be formed by a successive reaction of [III], and therefore, the reaction path that [IV] is a primary reaction product should be ruled out.

Figure 1 shows the effects of the composition of benzene or dioxane systems on the steric course of ethanolysis at 70 °C. The proportion of the retained product increased with an increase in the composition of co-solvents as is the case of acetonitrile, but the effect of benzene or dioxane was smaller

TABLE 4. ETHANOLYSIS OF [I] AT 50 °C

Solvent[a]	Time hr	Yield (%) [I]	[*threo*-II]	[*erythro*-II]	[IV]	[V]	Others	Ret. %
I	0.17	84	4	11	0	2		26
I	0.5	49	10	27	tr	4		27
I	1.0	27	16	44	0.6	7		26
I	1.33	16	19	54	1	7		26
I	1.67	8	20	56	2	7		26
I	3.0	1	21	60	3	6		26
I	3.3	tr	21	60	5	5		26
II	1.0	56	12	36	1	5	b)	24
II	2.0	17	19	53	6	7	b)	27
II	3.0	17	18	54	7	6	b)	25
II	4.0	9	20	56	9	5	b)	26
II	5.0	3	21	60	11	3	b)	26
II	7.0	tr	21	60	13	2	b)	27

a) I, pure ethanol; II, ethanol/hexane = 2:20 by volume b) Trace amounts of [VII] were observed.

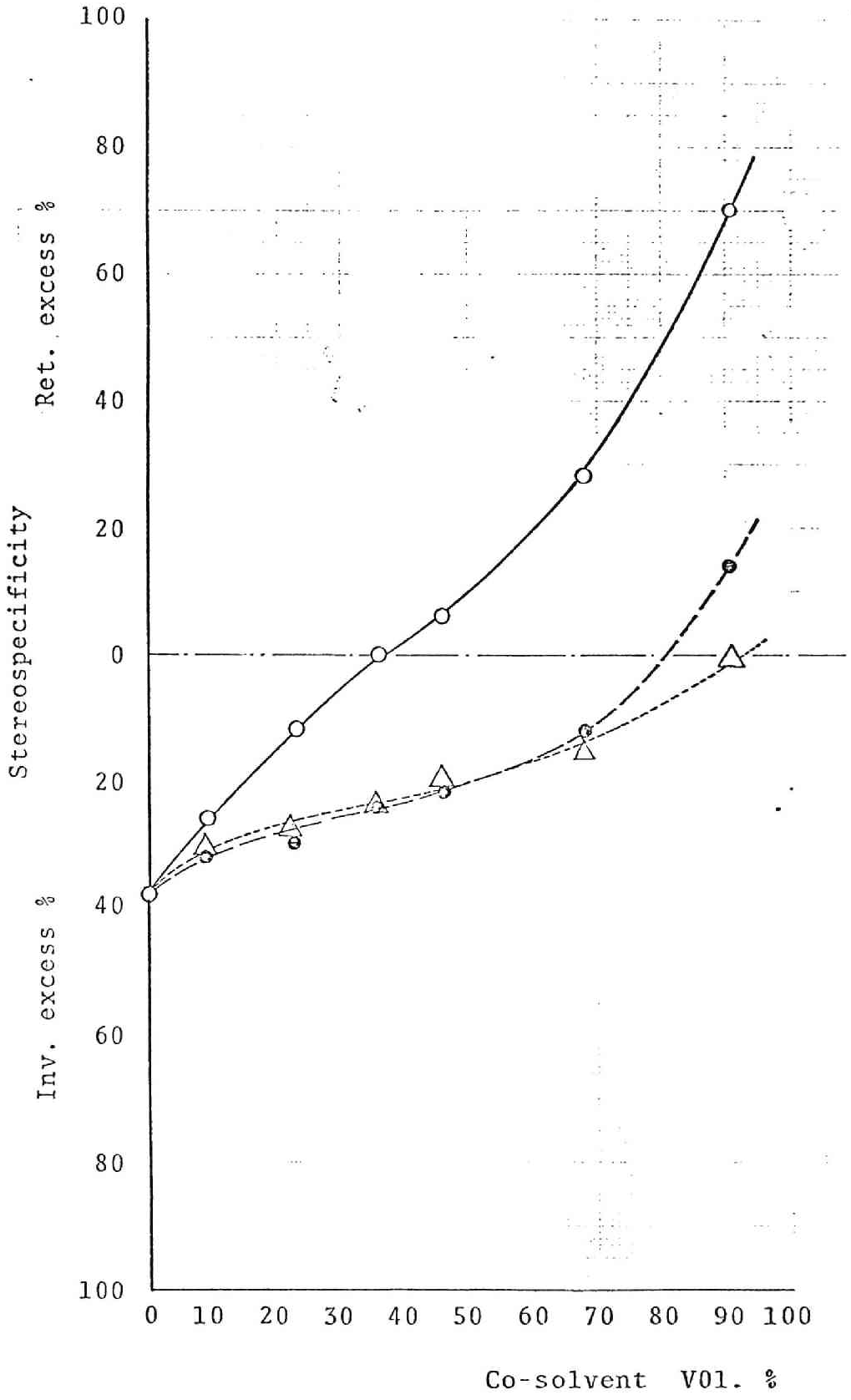


Fig. 1 Co-solvent effects on stereospecificity of the ethanolysis of 1 in binary solvent systems at 70 °C.

—○— : Acetonitrile, ——⊙—— : Dioxane, ----△----: Benzene.

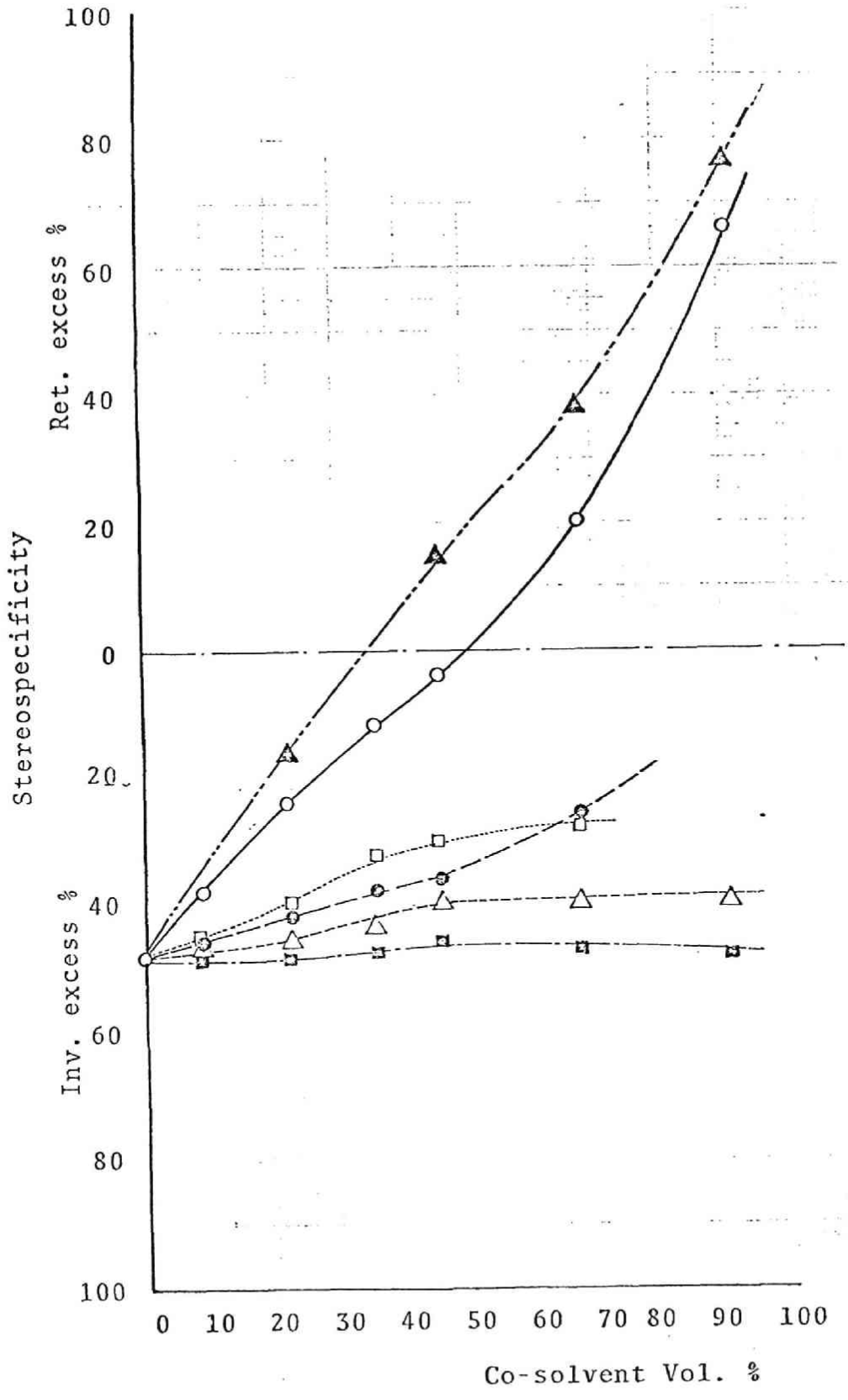


Fig. 2 Co-solvent effects on stereospecificity of the ethanolysis of 1 in binary solvent systems at 50 °C.

—○— : Acetonitrile, —·—○—·—: Dioxane, ·····□····· : Benzene,

—·—△—·— Nitromethane, ----△----: Mesitylene, —·—□—·—: Hexane.

than that of acetonitrile. The yields of the rearranged products were found to increase with an increasing proportion of co-solvent in the same manner as acetonitrile.

Figure 2 shows the effects of the composition of various solvent systems at 50 °C. With an increasing percentage of nitromethane, the proportion of the retained product increased, as is the case of acetonitrile, while stereochemical outcome of the ethanolysis was virtually unchanged when hexane was used as a co-solvent. Aromatic hydrocarbons and dioxane had slightly retentive effects. In every solvent systems, large amounts of the retained product were formed at a higher reaction temperature.

In Table 5 are presented the data of ethanolysis of [I] in binary solvent systems, ethanol-co-solvent (12:10 by volume). Quite different stereochemical results were observed with the choice of co-solvent. As the reaction proceeds quite slowly in DMSO, HMPA, and DMF, 10 times higher concentration of acid than in the other experiments was used. Very interesting nature of these co-solvents is that [I] gave larger amounts of inverted [II] in these systems than in pure ethanol. In all cases except these three co-solvents, total yields of the four compounds in scheme 1 were greater than 80%. By-products,[VI] [XI] were formed in some solvent systems. However, the yields of these by-products were less than 2%. When DMSO was used as co-solvent, the total yield decreased unexpectedly,

TABLE 5. ETHANOLYSIS OF [I] AT 50 °C IN ETHANOL-CO-SOLVENT (10:12 BY VOLUME) MIXTURES

Co-solvent	Reaction time hr	Yield (%) [I]	[*threo*- II]	[*erythro*- II]	[IV]	[V]	Others	Ret. %
Ethanol	8	0	22	63	11	1		26
		Hydrocarbons						
Hexane	4	tr	23	64	11	2		26
Cyclohexane	6	0	22	64	11	3		25
Benzene	5	6	26	49	16	tr	a	35
Toluene	6	0	26	54	16	4		33
m-Xylene	4	tr	25	54	19	tr	a	32
Mesitylene	6	tr	23	55	12	5	a	30
		Halides						
CCl_4	1	2	25	68	4	9	a,b,c,e	27
$CHCl_2CHCl_2$	6	34	11	21	2	2	a,b	33
		Ethers						
Bu_2O	6	0	22	63	12	3		25
THF	6	0	17	43	25	11	a,b	28
Dioxane	7	48	11	23	7	9		32
DME	6	0	22	45	15	12	a,d	33
Diglyme	6	10	18	34	16	13	a,b	34
		Ketone						
Acetone	6	0	26	40	18	2	a,b	40
		Nitrogen Compounds						
CH_3NO_2	4	0	39	29	32	tr		57

[Continued to the next page]

TABLE 5 Continued

Co-solvent	Reaction time hr	Yield (%) [*threo*-II]	[*erythro*-II]	[IV]	[V]	Others	Ret. %
$PhNO_2$	6	39	13	16	1	8	a,b,c	44
CH_3CN	8	12	31	34	4	14	c,e	48
PhCN[d]	6	–	–	–	–	–	–	41
DMF	72	32	2	10	0	2	a,b,e	19
		Sulfur Compounds						
DMSO	72	0	4	16	10	5	a-e	16
Sulfolane[d]	16	–	–	–	–	–	–	44
		Phosphorus Compound						
HMPA	16	24	3	29	0	7		10

a) Reactions were conducted with [I] (200 mg) in mixtures of ethanol (10 ml) and co-solvent (10 ml), and 2 ml of 0.01 N sulfuric acid solution in ethanol. When DMSO, DMF, and HMPA were used as co-solvents, 0.1 N sulfuric acid solution was used instead of 0.01 N solution. b) Yields were calcd on the basis of [I] used. c) The other products were as follows: a, benzyl phenyl ketone [VII]; b, 1-ethoxy-2,2-diphenylethene [VI]; c, 1,2-diphenylethanol [X]; d, 2-hydroxy-1,2-diphenylethanone[VIII], diphenylethanedione [IX] and/or 2,2-diphenylethanol [XI] e, unidentified products. d) Due to the difficulty of separation of solvent from internal standard on GC analysis, product yields could not be calculated.

TABLE 6. ETHANOLYSIS OF [I] AT 50 °C IN ETHANOL-SUBSTITUTED NITROBENZENE MIXTURES[a)]

	Yield (%)					Ret
Nitrobenzene (mmol)	[I]	[*threo*-II]	[*erythro*-II]	[IV]	[V]	%
Nitrobenzene (0.05)	0	28	44	9	9	39
Nitrobenzene (0.02)	0	27	56	16	1	32
p-Nitrotoluene (0.05)	0	28	47	9	9	37
p-Nitrotoluene (0.02)	0	26	55	16	1	32
m-Nitrotoluene (0.02)	0	26	54	16	1	32
m-Chloronitrobenzene (0.05)	0	27	44	7	9	38
m-Chloronitrobenzene (0.02)	0	26	55	17	1	32
p-Nitroanisole (0.02)	0	27	54	17	1	34

a) Reactions were conducted with [I] (200 mg) in mixtures of ethanol (10 ml) and nitrobenzenes (0.02 mmol or 0.05 mmol), and 2 ml of 0.1 M ethanolic solution of sulfuric acid. The amount of nitrobenzenes were given in parentheses.

but no other product than described above could be isolated.

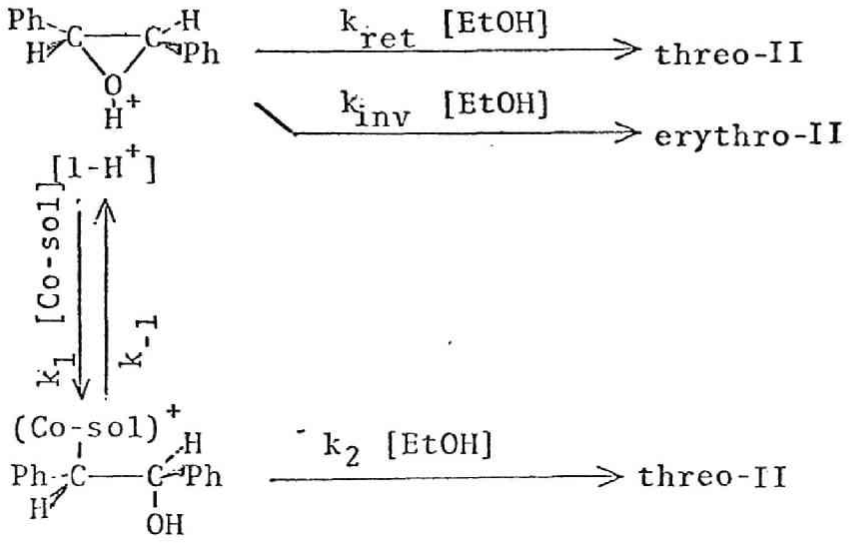
In Table 6 are presented the results of ethanolysis of [I] in mixtures composed of ethanol and substituted nitrobenzenes. As many of nitrobenzenes are solid and it was difficult to determine the volume ratios, experiments were carried out with fixed mol fractions.

3 Discussion

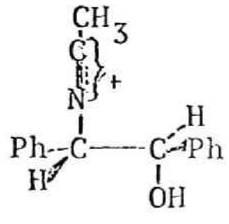
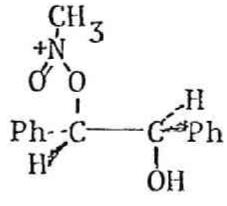
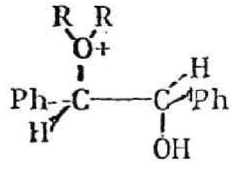
Several kinds of mechanisms have been proposed to explain the solvent effects on the steric course of solvolysis. At the outset, we shall examine whether these mechanisms can explain the present results or not. If Sneen's mechanism[2] is applied to this reaction, such a mechanism can be deduced that co-solvent participate from the back-side of epoxide ring at an ionizing stage of the epoxide C-O bond, as is shown in scheme 2.

However, when the applicability of this scheme to the experimental results is examined minutely (see appendix), the scheme meets a difficulty that the co-solvent should have stronger nucleophilicity to the conjugate acid of [I] than ethanol. On the other hand the scheme involves an assumption that co-solvent has no nucleophilicity to the co-solvent-participating intermediate [XII].

Experimental results mentioned above involve several kinds of data conflicting with the back-side shielding mechanism or the nucleophilic assistance mechanism.



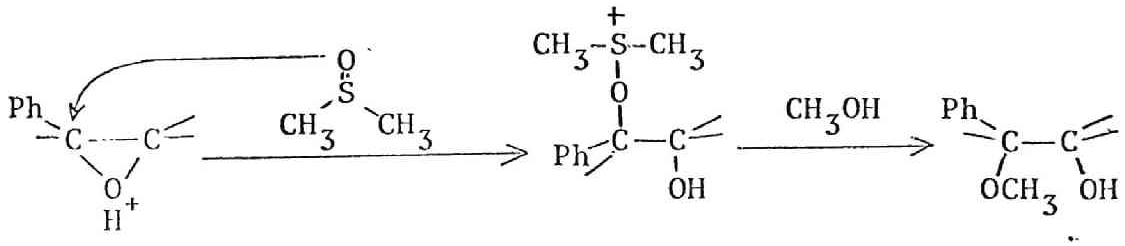
[XII]

[XII] ;  ,  ,  , etc.

Scheme 2

1. The proportion of the retained product decreased in the following orders of co-solvents: benzene > toluene > *m*-xylene > mesitylene, and nitrobenzene > *p*-nitrotoluene, which is inverse to the order of nucleophilicity.

2. Swern and his co-workers reported that DMSO reacts with epoxide to yield alkoxysulfonium salt which is the same type ion as the assumed intermediate [XII] and that this sulfonium ion reacts with alcohol to yield β-alkoxyalcohol (Eq. 3).[9]



(3)

However, the reaction of DMSO with epoxide requires much higher acid concentration than the ethanolysis experiments. When DMSO was used as co-solvent in the ethanolysis experiment, larger amounts of inverted product were formed than in pure ethanol. These facts make it difficult to assume the alkoxysulfonium ion as an intermediate of ethanolysis of [I] in DMSO.

3. Acetonitrile, nitromethane, and sulfolane, in which ethanolysis of [I] yielded large amounts of the retained product, are known as quite weak bases. Although no data are available to compare directly the nucleophilicity of the solvents toward a carbonium ion, coordina-

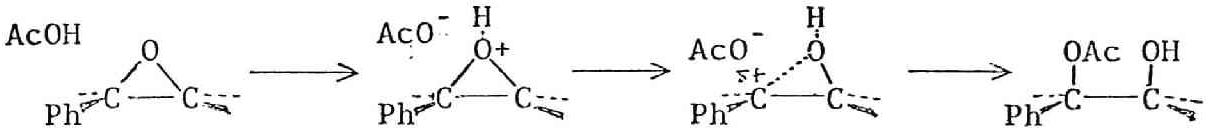
tion abilities of solvents to metal cations may afford some informations. At least, coordinating abilities of acetonitrile and nitromethane are much weaker than those of DMSO and DMF. Since nucleophilic participation of DMSO was disproved as mentioned above, it is improbable that acetonitrile and nitromethane, which are poorer nucleophiles than DMSO, participate in the ionizing stage of [I].

As none of the mechanisms proposed for solvolytic reaction can explain the experimental results, let us turn now to the mechanism of the epoxide reactions. Concerning the mechanism of ring-opening reactions leading to the formation of stereoisomeric products, Parker and Isaacs carefully discussed the reaction kinetics and stereochemistry and concluded that the concurrent reactions take place in these reactions, one of which gives a retained product and the other yields inverted one.[10] This proposal is widely accepted, and the results of the reaction of aryl-substituted epoxycyclohexanes reported by Italian workers also supports this concurrent reaction mechanism.[11] The results presented in this chapter, that the stereospecificity of the reaction varied from 80% inversion excess to 76% retention excess by changing co-solvent, appear to support Parker-Isaacs' conclusion, because the results would not be able to be explained by a single mechanism.

A short comment is added against S_N1 mechanism for epoxide reaction. By examining the entropies of activation

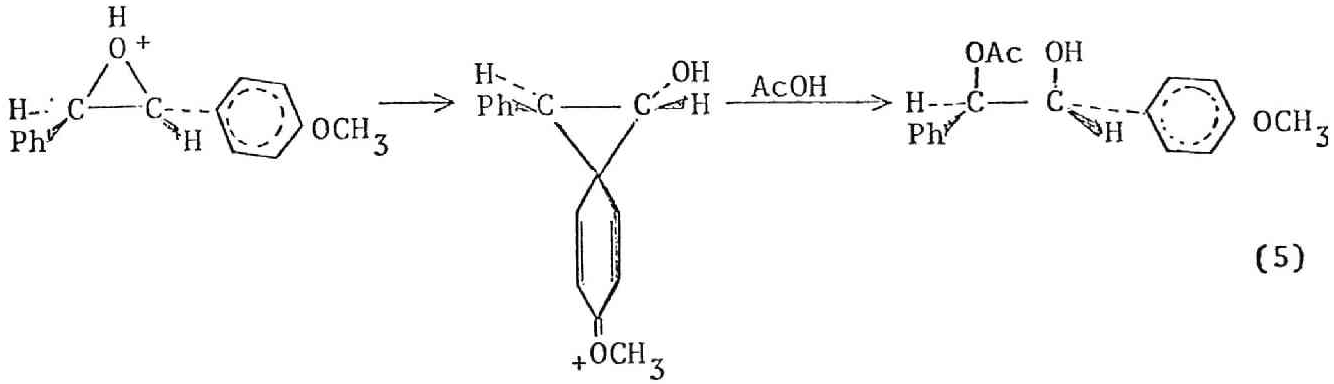
in the acid-catalyzed methanolysis of aryloxiranes, Chapman and his co-workers suggested that the reaction does not proceed *via* an unimolecular mechanism except in the case of 2,2-diphenyloxirane which shows a deviation towards an S_N1 mechanism.[12)]

Two mechanisms have been proposed for the retention reaction, one of the concurrent reactions. Brewster explained the retentive acetolysis of *trans*-2-methyl-2,3-diphenyloxirane in terms of an ion pair in a "cage" of solvent molecules (S_Ni mechanism, Eq. 4).[13)]



(4

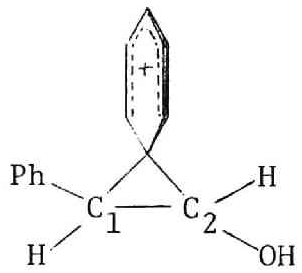
Another mechanism is a double inversion or a phenonium-iom mechanism (Eq. 5),[10)] and was proposed as a possible explanation for the results of acetolysis of 2-(*p*-methoxyphenyl)-3-phenyloxirane.[14)] Recently Ito found, however,



(5)

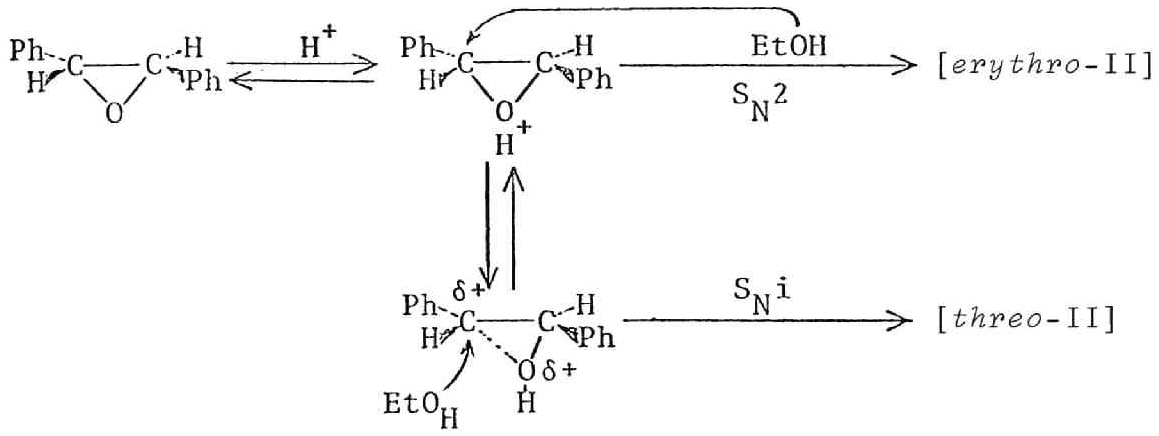
that the position attacked by acetic acid is not benzyl carbon but anisyl one of that compound.[15] To explain this result by a phenonium-ion mechanism, the participating group should not be methoxyphenyl but phenyl group, which is an unlikely process to occur.

Although phenonium-ion mechanism have been employed by many workers, there is no clear evidence to confirm the existence of the phenonium ion substituted by heteroatoms. If double inversion mechanism were true for the present case, the phenonium ion [XIII] depicted below should exist as an intermediate and react with ethanol. The existence of this intermediate appears to be unlikely, when the following processes are taken into account. When bridging phenyl group moves from the center of two carbon atoms (C_1, C_2) toward C_1 atom, a developing p-orbital at C_2 carbon atom can conjugate with lone pair of oxygen atom adjacent to C_2 carbon atom, and the cation gains additional stabilization energy. At the end of this drift, an oxonium ion of the conjugate acid of aldehyde is formed which is well established to be more stable than phnonium ion by kinetical evidence.[16] As a result, the phenonium ion, if it were to be formed, is not an intermediate of the retentive solvolysis but the transition state of the rearrangement to [III].



[XIII]

As is summarized in Table 7, stereochemical results of acid-catalyzed solvolysis of [I] are closely related to those for optically active 2-phenyloxirane. Here, phenonium ion cannot be an intermediate of solvolysis of 2-phenyloxirane, since nucleophiles attack the benzyl carbon atom. Thus it is unreasonable to consider that the phenonium ion is the intermediate of solvolysis of [I], and the author concludes that an S_Ni (ion pair) mechanism opperates in the retentive ethanolysis which is one of the concurrent reactions of [I] (scheme 3).



Scheme 3

As parker and Isaacs pointed out,[10] the transition state depicted by Brewster is similar to the borderline S_N2 mechanism with the added proviso that the reagent is held close to the epoxide oxygen by electrostatic forces. However, the author considers that the transition state of retentive ethanolysis of [I] has a stronger tendency toward

TABLE 7 STEREOCHEMICAL RESULTS OF THE ACID-CATALYZED SOLVOLYSIS OF ARYLOXIRANES

	Alcoholysis	Hydrolysis
2-Phenyloxirane	11% ret-89% inv[a)]	50% ret-50% inv[b)]
trans-2,3-Diphenyloxirane	26% ret-73% inv[c)]	60% ret-40% inv[d)]

a) Methanolysis at 22.8 °C, J. Biggs, N. B. Chapman, and V. Wray, *J. Chem. Soc. (B)*, 1971, 71. b) Suspention, C. Dupin and J.-F. Dupin, *Bull. Soc. Chim. Fr.*, 1970, 249.

c) Ethanolysis at 50 °C, this work. d) Extrapolation value from the results on hydrolysis in mixtures of water and various kinds of co-solvents, see chapter VII.

an S_N1 mechanism than that of borderline S_N2 reaction giving the inverted product, and will discuss in the following chapter.

In Table 8, the stereochemical results in binary solvent systems are given together with dielectric constants, pKa of conjugate acid,[17] and E_T values[18] of the co-solvents. No direct relationship can be found between the stereochemical results and the physical properties of co-solvents. However, detailed examination of Table 8 suggests that co-solvents can be classified into three groups. The first group (group 1) contains acetonitrile, nitromethane, sulfolane,[19] etc., which have poor basicities and high dielectric constants, and in which the ethanolysis of [I] yields large amounts of retained product. The second group (group 2) solvents have poor basicities and low dielectric constants, and these co-solvents have no effects or slightly retentive effects on the ethanolysis of [I]. The third group (group 3) contains aprotic polar solvents such as DMSO, DMF, and HMPA. The difference between the aprotic polar solvents and those of the first group is that the former have much more basic characters, therefore higher coordinating abilities than those of the first group.

To discuss the function of co-solvent in ethanolysis of [I], we have to know the nature of solvation. Solvation shells are most often discussed in terms outlined in Gurney's influential book[20] as region A, B, and C.

TABLE 8. CO-SOLVENT EFFECTS ON ETHANOLYSIS OF 1[a] AND PHYSICAL PROPERTIES OF CO-SOLVENTS

Co-solvent	Ret.[b] %	Rearr.[b] %	e	pKa of conjugate acid	E_T	
CH_3NO_2	56	32	35.87	-11.7	46.3	group 1
CH_3CN	48	22	37.5	-10.13	46.0	
Sulfolane	44	23	43.3		44.0	
$PhNO_2$	44	24	34.82	-10.39	42.0	
PhCN	41		25.2	-10.45	42.0	
Acetone	40	23	20.7	-6.5	42.2	
Benzene	35	17	2.275		34.5	group 2
Diglyme	34	36				
DME	33	29	7.20	-3.27	38.2	
$CHCl_2CHCl_2$	33	12	8.20			
Toluene	33	20	2.379		33.9	
Dioxane	32	32	2.207	-3.22	36.0	
m-Xylene	32	19	2.374			
Mesitylene	30	17	2.279			
THF	28	38	7.85	-2.08	37.4	
CCl_4	27	12	2.238		32.5	
Hexane	26	12	1.8799		30.9	
Bu_2O	25	15	3.083	-5.40		
Cyclohexane	25	14	2.023			
DMF	20		52.1	(-0.19)[c]	43.8	group 3
DMSO	16		44.68	0	45.0	
HMPA	10	21	30			
Ethanol	26	12	24.55	(-2.2)[d]	51.9	

a) See foot note a) of Table 5. b) See foot notes b) and c) of Table 1. c) pKa of the conjugate acid of dimethyl acetamide. d) pKa of the conjugate acid of methanol.

Region A is one of high order imposed by the influence of the solute on nearby solvent molecules. Region C is a region of unaltered bulk solvent. Region B is a "disordered" compromise region which is influenced comparably both by the force exerted by the solute which produce region A near the solute and by the solvent-solvent forces which produce region C in the bulk far from the solute.[21]

For the mechanistic purposes, Gurney's classification will be modified[22] and extended to the solvation of proton in binary solvent mixtures. Region A is defined as a primary coordination sphere. In region A, the proportion of the solvent with strong basicity, *i.e.* high coordinating ability to proton, should be larger than in the whole solvent system. For example in ethanol-acetonitrile system, the proportion of ethanol in region A should be larger than in the bulk solution, since ethanol is stronger base than acetonitrile. In ethanol DMSO system, the proportion of DMSO in region A is larger, since DMSO is stronger base than ethanol. Region C is a bulk region, in which the composition of solvents is the same as the composition of whole solvent system. Region B is defined as a transition region between region A and region C, and influenced by many kinds of forces. Among them, charge-dipole interaction which is a long-range intermolecular force seems to be most important in the present case. It is difficult to estimate the composition of solvents in region B of binary solvent systems, since the nature of

charge-dipole interaction in solution is not yet clear. However we wish to point out simply that the proportion of the solvent of high dielectric constant should be higher in region B than in the bulk solution, because effects of dielectric field of proton can be relaxed by the dielectric polarizability of solvent. The discussion is clearly oversimplified, but is able to explain the stereochemical results.

As mentioned above, it is well established that initial protonation is a fast reversible step in the acid-catalyzed ring-opening reaction of epoxide. Around the proton of the protonated epoxide, solvent molecules build up region A,[23] and the back side of epoxide ring borders on region B.[24,25] Ethanol proportions in two regions A and B differ by the influence of basicity and dielectric polarizability of co-solvent, and therefore effective concentrations of ethanol in the both sides of epoxide differ in the *ground state* of ethanolysis. In other words, effective concentrations[26] of ethanol for S_Ni and S_N2 reactions differ to each other, and this difference results in the changes of the steric course of ethanolysis of [I].

On the basis of above discussion, each cases of the stereochemistry of ethanolysis can be explained as follows. In binary ethanolic mixtures containing group 1 co-solvents, effective concentration of ethanol in the front-side of the epoxide is much higher than in the back-side of the epoxide,

because the proportion of co-solvent in region B and that of ethanol in region A are higher than those in whole solvent systems. Consequently ethanolyses of [I] in these solvent systems yield larger amounts of retained product than in pure ethanol.[27] In binary ethanolic mixtures containing group 3 co-solvents, strong basicity of co-solvent results in an increase of co-solvent proportion in region A, and in a decrease of effective concentration of ethanol in the front-side of epoxide, and ethanolyses of [I] in ethanol-group 3 co-solvent mixtures yield larger amounts of inverted product. In binary ethanolic mixtures containing group 2 co-solvents, which have low dielectric constant, the probability of existence of the group 2 co-solvents in region A and B is low, because two regions are in the dielectric field of positive charge. As a result, steric course of ethanolysis of [I] in these solvent mixtures is quite similar to that in pure ethanol.

The discussion mentioned in this chapter may not be limited to the epoxide reaction, and Streitwieser and Doering's results quoted at the beginning of this chapter can be explained along the same line.

Medium effects on the steric course of the acid-catalyzed hydrolysis of [I] are discussed in the subsequent chapter.

4 Experimental

Materials. *trans*-2,3-Diphenyloxirane [I] was prepared by *m*-chloroperbenzoic acid oxidation of *trans*-stilbene and recrystallized from hexane and then from benzene, mp. 68.5-69.5 °C (lit,[28] 69.0-69.5 °C). Ethanol was dried by Lund and Bjerrum's method.[29] All the co-solvents were dried by the most efficient ways appeared in the literature[30] and distilled before use.

erythro-*2-Ethoxy-1,2-diphenylethanol* [erythro-*II*]. A mixture of *meso*-1,2-diphenyl 1,2-ethanediol[31] (2.0 g) and triethyloxonium tetrafluoroborate (2.66 g) in dry ether (100 ml) was stirred for a day at room temperature, poured into water, and extracted with ether. The ether layer was dried over sodium carbonate, and removal of the solvent gave 1.3 g of white solid. GC analysis indicated that it contained three products. After the separation of the products by column chromatography, [*erythro*-II] (117 mg) was obtained from the middle fraction, mp. 52.5-53.5 °C (lit,[32] 45-50 °C). NMR ($CDCl_3$) δ: 1,1^0 (3H, t, *J*=7 Hz), 2.4^7 (1H, d, *J*=4 Hz OH), 3.3^7 (2H, AB part of ABX_3 coupling), 4.4^0 (1H, d, *J*=5 Hz), 4.8^3 (1H, d.d), 7.1^3 (10H, phenyl). Found: C, 79.47; H, 7.56%. Calcld for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%. The other products were the starting material and *meso*-1,2-diethoxy-1,2-diphenylethane.

threo-*2-Ethoxy-1,2-diphenylethanol* [threo-*II*]. 2-Ethoxy-1,2-diphenylethanone was reduced with sodium boro-

hydride as the usual way. GC analysis indicated that the crude product was composed of two components with a ratio 87:13. The crude product was column chromatographed. The major product was consisted with [*erythro*-II], and [*threo*-II] was obtained as the minor one and did not form crystals after several months. NMR ($CDCl_3$) δ: 1.2[1] (3H, t, J=7 Hz), 1.7 (1H, s, OH), 3.3[9] (2H, q), 4.1[8] (1H, d, J=8 Hz), 4.5[8] (1H, d), 7.0[7] (10H, phenyl). Found: C, 79.32; H, 7.52%. Calcld for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49%.

Ethylation of *dl*-1,2-diphenyl-1,2-ethanediol by the oxonium salt resulted in only recovery of the starting material.

1,1-Diethoxy-2,2-diphenylethane [*IV*]. To a solution of [III][33] (2.0 g) in 70 ml of abs ethanol, a drop of concd sulfuric acid was added. The reaction mixture was stirred for a day at room temperature. GC analysis of the reaction mixture indicated 97% conversion to [VI]. Distillation of the neutralized mixture gave 1.6 g of [IV]: bp 117-119 °C/2.5 mmHg: IR 1060 and 1120 cm^{-1}: NMR ($CDCl_3$) δ: 1.0[3] (6H, t, J=7 Hz), 3.5 (AB part of ABX_3 coupling $\Delta\nu$=10 Hz, J_{AB}=9.3 Hz, J_{AX}=6.8 Hz, J_{BX}=7.2 Hz, 4H), 4.2[3] (1H, d, J=7.8 Hz), 5.0[5] (1H, d), and 7.3[0] (10H, phenyl). When anhydrous copper (II) sulfate was used for acetallization instead of sulfuric acid, initially formed [IV] was converted to [VI][34] before acetallization was completed.

Ethanolysis of [*I*] *in Pure Ethanol*. To a 20 ml ethanolic solution of weighed quantities of [I] and dibenzyl

ether (internal standard) held in a controlled-temp block, 2 ml of acidified (H_2SO_4) ethanol was added with vigorous shaking. After a definite period, 0.5 ml of reaction mixture was pipetted out into a sampling tube containing a small amount of K_2CO_3, and the tube was shaken vigorously. The quenched sample was kept at room temp for a day, and analyzed by GC.

Ethanolysis of [I] in Binary Solvent Systems. To a 10 ml ethanolic solution of [I] (200 mg) and dibenzyl ether (30-50 mg, weighed), 10 ml of the co-solvent was added, and the mixture was held in a controlled-temp block. Ethanolic solution of sulfuric acid (2 ml, *ca* 0.01 N)[35] was added to the mixture and then treated as mentioned above.

GC Analyses. The GC analyses (Hitachi 163 gas chromatograph) were carried out successfully on a 4 m column of 5% PEG-20M on Shimalite W at a column temp of 205 °C. For example, the retention times of dibenzyl ether, [IV], [V], [VI], [III], [*threo*-II], [VII], [*erythro*-II], [VIII], and [IX], [X] and/or [XI] were 9.3, 11.4, 12.3, 14.6, 15.2, 18.2, 20.3, 23.8 25.8 and 31.2 min respectively.

Autoxidation of [III]. To a solution of freshly prepared [III] (910 mg) in ethanol (10 ml), a catalyst was added. The reaction mixture was kept at room temp for a day, and was subjected to GC analysis. The conversions of [III] to [V] (cat; a small amount of K_2CO_3, a small amount of Na_2CO_3, 0.1 ml of 0.1N H_2SO_4 in ethanol, and none) were 100, 53, 0.3% and trace.

5 Appendix

From the reaction sequence described in scheme 1, following equations can be obtained

$$\frac{d[\textit{threo}\text{-II}]}{dt} = k_{ret}[EtOH][I\text{-}H^+] + \frac{k_1 k_2 [Co\text{-sol}][I\text{-}H^+][EtOH]}{k_2[EtOH] + k_{-1}}$$

$$\frac{d[\textit{erythro}\text{-II}]}{dt} = k_{inv}[EtOH][I\text{-}H^+]$$

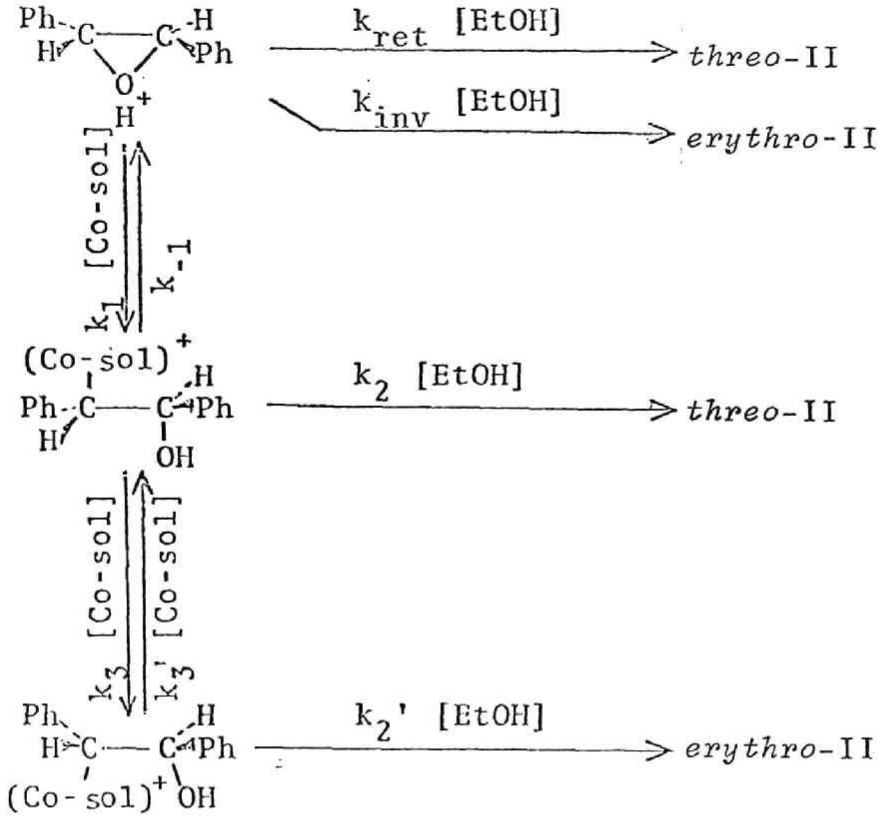
Therefore $$\frac{[\textit{threo}\text{-II}]}{[\textit{erythro}\text{-II}]} = \frac{k_{ret}}{k_{inv}} + \frac{\frac{k_1}{k_{inv}}[Co\text{-sol}]}{[EtOH] + \frac{k_{-1}}{k_2}}$$

If the effective concentrations in reaction kinetics are the same as the molar concentrations of the medium, values 0.48, 2.04, and 0.55 for k_{ret} / k_{inv}, k_1 / k_{inv}, and k_{-1} / k_2 respectively, can satisfy the experimental results presented in Table 2 except for the case of 91% of acetonitrile concentration.

However, the value 2.04 for k_1 / k_{inv} means that the nucleophilicity of acetonitrile to the conjugate acid of [I], $[I\text{-}H^+]$, is stronger than that of ethanol, whereas the reaction scheme includes an assumption that co-solvent, as compared with ethanol, has negligibly small nucleophilicity to the intermediate [XII].

As it is difficult to consider that the strength order of nucleophilicities of ethanol and acetonitrile toward $[I\text{-}H^+]$ is inverse to the order toward [XII], the co-solvent should

have nucleophilicity to [XII]. Then, the reaction scheme becomes as follows (scheme 4).



Scheme 4

The meanings of this reaction-scheme are quite similar to Streitwieser's. However, a solution of the reaction kinetics with the use of steady state method leads to the same difficulties mentioned above, because the experimental results are satisfied only when $k_1 > k_{inv}$ and $k_2 > k_3$.

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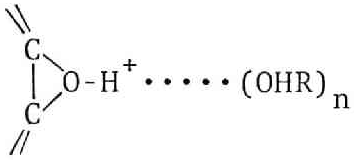
23) Major parts of solvation energies should come from hydrogen bonding from acidic hydrogen of the conjugate acid epoxide to "bulk ethanol",



For a detailed discussion of hydrogen bonding from the hydrogen of onium ion to "bulk water", see for example; E. M. Arnett, B. Chawla, L. Bell, M. Taagepera, W. J. Hehre, and R. W. Taft, *J. Am. Chem. Soc.*, 99, 5729 (1977).

24) A variety of the values for the solvation number of proton have been reported; 1-2,[a] 2.5,[b] 3.9,[c] 5,[d] and 10.[e] The oxonium ion [I-H^+] in solution can be considered to be formed by substitution of one of the solvent molecules in solvation shell of proton (region A) for the epoxide. As the first solvation shell of proton (region A) is small, the back-side of [I] borders on region B.

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25) These structure of solution are easily fading, but have enough life time for epoxide to be attacked in these solution structures, because acidic hydrogen should exist at

the epoxide oxygen during the reaction.

26) A similar concept has been discussed in terms of preferential solvation, see ref. 21.

27) If ethanol molecules in region A are completely oriented by the effect of charge of proton, nucleophilicity of the ethanol should be much lower than that of ethanol in region C. However, this problem can be solved by Backrins-Saluja's model for solvation, in which coordination number is always larger than solvation number.[a] In other words, they pointed out the existence of non-solvated coordinated molecules in region A. In the present case, the non-solvated coordinated ethanols in region A have ordinary nucleophilicity to [I] to yield the retained product.

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35) A definite concentration of sulfuric acid solution in ethanol (0.01 N) was prepared initially, but the correction factor decreased gradually on storage. However, the stereochemical results of ethanolysis of [I] in binary solvent systems were not affected by the acid concentration.

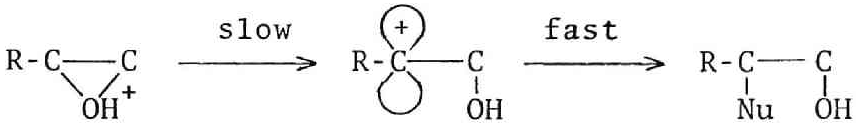
CHAPTER VI Temperature Effects on the Stereochemistry of Solvolysis of an Epoxide

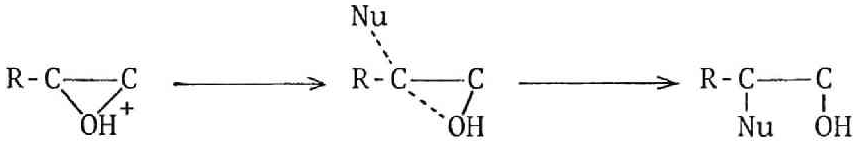
Temperature effects on the stereochemistry of the acid-catalyzed ethanolysis of *trans*-2,3-diphenyloxirane were examined. The stereochemistry of the reaction became more retentive as reaction temperature was raised. Reaction mechanisms are discussed, and it is concluded that concurrent reactions take place in the ethanolysis one of which gives a inverted product and the other yields retained one, and that the former reaction is caused by a nucleophilic attack of ethanol on the carbon of the conjugate acid of the epoxide and the latter proceeds *via* an intermediate which have a carbonium ion character.

1 Introduction

Nucleophilic ring-opening reactions of epoxide have been widely studied. The following observations indicate that epoxides react by S_N2 mechanism in basic conditions; (1) Nucleophiles attack the least substituted carbon atom of epoxide ring. (2) The reactions conform to a second-order rate low. (3) Inversion of configuration takes place at the carbon atom attacked by nucleophiles (*trans*-ring-opening).

The mechanism of ring-opening of epoxides in acidic media is a quite complex matter. It is now generally accepted that the initial protonation to epoxide oxygen atom is a fast reversible step.[1] In the limiting form, two mechanisms are possible for the ring-opening and the attack of nucleophile.

A1 mechanism 

A2 mechanism 

A number of kinetical studies have appeared concerning the acid-catalyzed solvolysis of epoxide. As the attacking nucleophile is the solvent, both mechanisms lead to the same rate expression. Thus alternative criteria have been used, and were carefully discussed by Chapman and his co-workers. Long *et al.*,[2] following a suggestion by Taft and his co-workers,[3] proposed the use of $\Delta S^{\ddagger}$ as a criterion for the mechanism of hydrolytic reaction. Entropies of activation for acid-catalyzed hydrolysis of simple epoxides are between -6.1 and 3.9 cal mol^{-1} K^{-1},[4] which are much lower than those of the reaction of established A1 mechanism and yet greater than those of established A2 mechanisms, and these values are explained in terms of a borderline A2 mechanism.[5]

Nucleophilic attack by an A2 mechanism involves inversion of configuration, while an A1 mechanism involves racemization in the limiting form. It is widely recognized that simple aliphatic epoxides give inverted products in acid-catalyzed ring-opening. Only one exception is the reaction of 2,3-epoxybutane with aluminum chloride in nitromethane which yields more than 85% retained 2-chloro-1-butanol.[6]

In aryl or carbonyl substituted epoxides, reactions are also known in which epoxides ring-open with retention of configuration at the position attacked. In a few epoxides, ring-openings give rise to both stereoisomeric products. Parker and Isaacs concluded that concurrent S_Ni and S_N2 mechanisms take place in the reactions of this type.[5]

Recently Chapman and his co-workers have studied the acid-catalyzed ethanolysis of styrene oxide both kinetically and stereochemically.[7] The reaction yields a mixture of 89% inversion and 11% retention products at 23 °C. They explained their observations by only a borderline A2 mechanism involving the transition states depicted in scheme 1. Obviously two transition states which have different situations around the carbon atom attacked are different in energy. Then the reaction parameters, activation enthalphy and activation entrophy, are different for two reactions, one of which yields retained product and the other gives

inverted one. As two reactions have different activation parameters to each other, it is ridiculous why they could discuss the two reactions in terms of single pair of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. Stereochemical outcome should be altered by variation of reaction temperature. However, they did not explore the temperature effects on stereochemistry.

Although a number of papers, including those of Chapman *et al.*, have discussed the temperature effects on reaction kinetics, *i.e.* activation parameters, only a few papers dealt with the effects on stereochemistry. Two contrasting results appeared in the literature. Fisher and Koch reported acid-catalyzed hydrolysis of *trans*- and *cis*-2-methyl-3-phenyloxirane in aqueous dioxane.[8] The reaction afforded 67% inverted glycol from the trans epoxide and 76% inverted one from the *cis*-isomer, and the stereochemistry of the reaction did not change at the temperature range of 20-45 °C. From these results, one can expect that the reaction has only one transition state yielding both retained and inverted products.

On the other hand, Macchia *et al.* reported that the acid-catalyzed solvolysis of 1-aryl 1,2-epoxycyclohexane afforded larger amounts of retained product at higher reaction temperatures.[9] From this observation, one can expect that the concurrent reactions take place, one of which leads to inverted product and the other to retained one. This chapter reports the temperature effects on the

stereochemistry of ethanolysis of *trans*-2,3-diphenyloxirane (I)[10] and discusses the mechanism of the reaction.

2 Results and Discussion

In the study of the stereochemistry of the acid-catalyzed ethanolysis of (I) at the temperature range below the boiling point of ethanol, the same experimental conditions were chosen as those in the foregoing chapter. The results are summarized in Table 1. The proportion of the retained product, *threo*-2-ethoxy-1,2-diphenylethanol (*threo*-II), increased as the reaction temperature was raised. Similar temperature effects were observed in the experiments in binary solvent systems.

To examine the stereochemistry of the reaction at the temperature higher than the boiling point of ethanol, experiments were carried out in an autoclave. Unexpectedly, sulfuric acid which was used as a catalyst in experiments of Table 1 and of the foregoing chapter has no catalytic activity at the temperature range higher than 130 °C, and only starting material (I) accompanied with traces of 1,2-diphenylethanol (VIII) and 1,1-diphenylethanol(IX), 1,2-diphenyl-2-hydroxyethanone (X), and/or diphenylethanedione (XI) was detected on GC analysis when ethanol solution of (I) containing sulfuric acid was allowed to stand at 200 °C for 4 h. This observation may be attributed to the fact that sulfuric acid acts as an oxidizing agent and reduced material

TABLE 1. TEMPERATURE EFFECTS ON THE ETHANOLYSIS OF (I)

Reaction temp	Solvent	Product Distribution (%) (IV)	(V)	(*threo*-II)	(*erythro*-II)	Retention[a] (%)
30	EtOH	8	tr.	18	74	20
50	EtOH	12	tr.	23	65	26
70	EtOH	16	tr.	26	58	31
50	EtOH-CH_3CN (46:54, vol.)	9	15	36	40	48
70	EtOH-CH_3CN (46:54, vol.)	18	12	37	33	53

a) The proportion of (*threo*-II) to the total (II).

of sulfuric acid has no catalytic activity toward the ethanolysis. Therefore, hydrochloric acid was used as the catalyst for the experiments of higher reaction temperatures. Typical results were given in Table 2. As shown in Table 2, larger proportions of the retained product were observed at higher temperatures, and almost equal amounts of retained and inverted products were formed at 200 °C. Although it is interesting whether the proportion of the retained product increases monotonously or not at more higher temperatures, clear-cut results were not obtained because of the formation of undesired products, *i.e.* rearranged products; diphenylacetaldehyde (III), diethyl acetal of the aldehyde (IV), 1-ethoxy-1,2-diphenylethene, and benzyl phenyl ketone (VII); and oxidation-reduction products; (VIII), (IX), (X), and (XI). It must be noted that the yields of (VII) increased suddenly at the temperature higher than 160 °C, which was reported not to be formed in the rearrangement by acid.[11]

Higher acid concentration gave more inverted product, which forms a striking contrast to the results mentioned in the foregoing chapter. Four reasons can be considered; (I) effects of a trace of water contaminated in acid solution, (2) contamination of non-acid-catalyzed reaction which yields retained product, (3) formation of chlorohydrin, or the subsequent ethanolysis of the chlorohydrin, (4) effects of ion-pairing of the acid. To examine the effects of water, reactions were carred out with small amounts of water

TABLE 2. TYPICAL RESULTS OF ACID-CATALYZED ETHANOLYSIS OF *trans*-2,3-DIPHENYLOXIRANE AT HIGH TEMPERATURES.

temp (°C)	time (h)	acid[c] (μl)	product distribution[a] (%)								retention[b] (%)
			(I)	(IV)	(V)	(*threo*-II)	(*erythro*-II)	(VI)	(VII)	others	
90 ± 2	4	100	37.3	0.4	1.1	18.5	41.7	0.6			29.6
103 ± 1	4	100	29.2	1.3	1.0	22.9	45.1	0.5			33.7
120 ± 3	3.5	100	22.1	3.2	2.3	27.1	43.8	0.6		0.1	38.9
130 ± 2	3	100	17.9	5.0	1.1	30.7	44.7	0.6		tr.	40.7
140 ± 1	3	80	18.9	5.5	1.3	30.7	42.6	0.7			41.9
149 ± 1	2	100	19.8	6.1	0.5	30.7	42.9	tr.			41.3
165 ± 1	2	100	5.7	16.1	0.8	30.9	39.5	1.1	5.9		43.9
190 ± 4	2	75	22.0	4.3	3.6	30.3	36.2	3.2		0.4	45.6
206 ± 3	2	20	57.9	0.2	4.9	13.9	14.8	5.7		2.6	48.4
220 ± 3	2	50	28.5	3.0	3.2	28.3	29.4	3.9	1.2	2.1	49.1
130 ± 2	3	200	0.4	10.6	0.5	28.0	50.9	0.4	9.2		35.5
130 ± 2	3	150	0.7	15.3	0.4	28.6	48.3	0.4	6.3		37.2
130 ± 2	3	80	25.5	2.7	1.7	28.1	41.0	0.8		0.2	40.7
130 ± 2	3	50	49.3	0.3	1.4	19.7	28.6	0.7			40.8
130 ± 2	3	30	68.9	0.1	0.8	12.2	17.7	0.6			41.3

a) Determined by the relative area ratio on GLPC. b) 1,2-Diphenylethanol, 2,2-diphenylethanol, diphenylethanedione, and 2-hydroxy-1,2-diphenylethanone. c) Hydrochloric acid solution (0.005 mol/l) in ethanol was added to 1 ml of ethanol solution containing 10 mg of *trans*-2,3-diphenyloxirane.

added. Results are shown in Figure 1. As the proportion of the retained product increased with an increasing amount of water added, the reason (1) can be excluded. The reason (2) is easily excluded because no reaction occurred without acid catalyst. The reason (3) is recently proposed by Whalen *et al.* as specific effects of chloride ion in the hydrolysis of phenanthrene 9,10-oxide,[12] and can not be completely excluded in the present case, although no chlorohydrin was detected in the reaction products and chloride ion concentrations are a hundred times as small as those of (I). The reason (4) is proposed by Wylde and his co-workers,[13] and seems to be the most probable explanation for the present case. As the counter anion exists near the protonated oxygen in ion pair of protonated epoxide and chloride, probability of existance of ethanol in the front side of the epoxide ring decreases as compared with free ion, and inversion reaction are favored by the ion pair. As the dilution of acid solution causes the ion pair to dissociate into free ions, the reaction becomes more retentive with lowering acid concentrations.

As the stereochemistry of the ethanolysis is affected by the reaction temperatures, two reactions are expected to take place in the ethanolysis. If Parker-Isaacs conclusion is true, overall kinetical expression is as follows;

$$k_{obs} = k'K[H^+] = (k_{ret} + k_{inv})K[H^+]$$

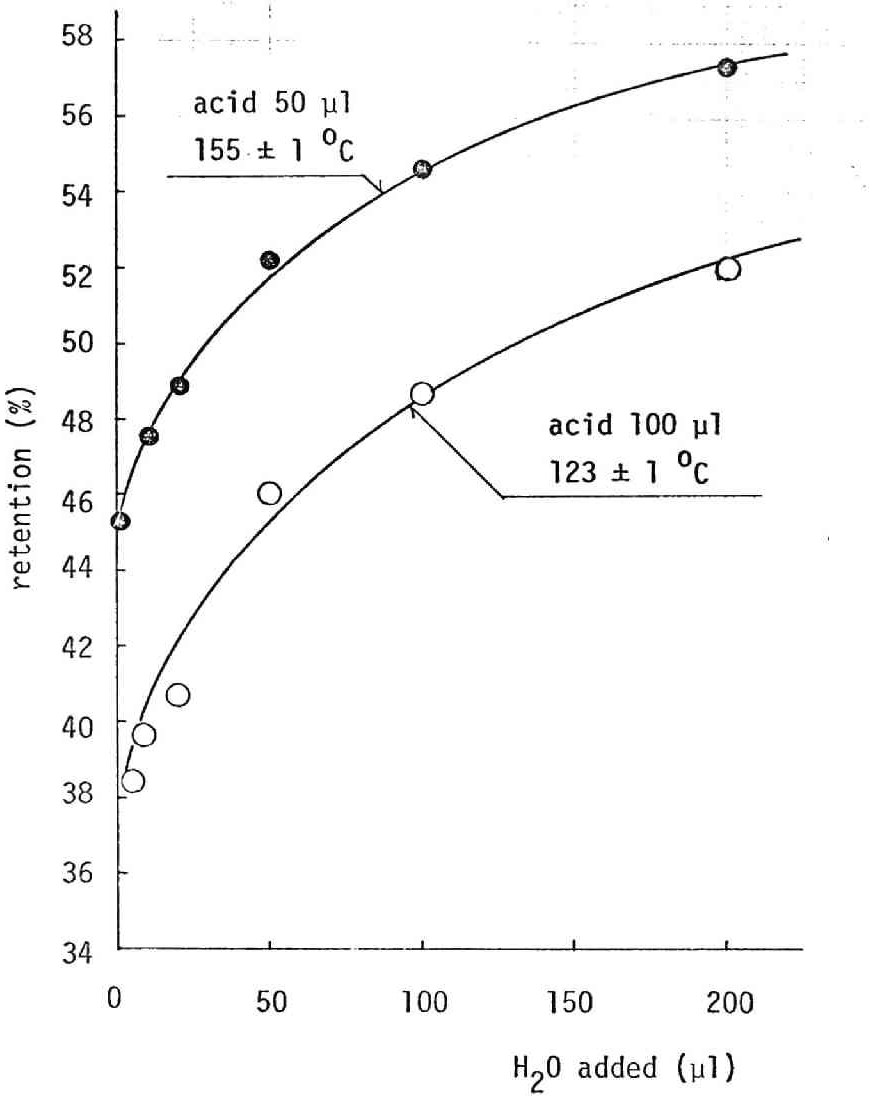


Fig. 1. Effects of water on ethanolysis of *trans*-2,3-diphenyloxane

in which k_{ret} is a second order rate constant for the reaction which gives retained product and k_{inv} is that for inversion reaction. Then reaction parameters for each of the reactions can be defined as;[14]

$$k_{ret} = \gamma \exp\left(\frac{-\Delta G^{\ddagger}_{ret}}{RT}\right) = \gamma \exp\left(\frac{T\Delta S^{\ddagger}_{ret} - \Delta H^{\ddagger}_{ret}}{RT}\right)$$

$$k_{inv} = \gamma' \exp\left(\frac{-\Delta G^{\ddagger}_{inv}}{RT}\right) = \gamma' \exp\left(\frac{T\Delta S^{\ddagger}_{inv} - \Delta H^{\ddagger}_{inv}}{RT}\right)$$

Therfore

$$\frac{k_{ret}}{k_{inv}} = \frac{\gamma}{\gamma'} \exp\left(\frac{\Delta S^{\ddagger}_{ret} - \Delta S^{\ddagger}_{inv}}{R}\right) \exp\left(-\frac{\Delta H^{\ddagger}_{ret} - \Delta H^{\ddagger}_{inv}}{RT}\right)$$

Assuming that the activation parameters are constant at the temperature range of the experiments, the following equation can be deduced;

$$\ln\left(\frac{k_{ret}}{k_{inv}}\right) = \frac{\Delta H^{\ddagger}_{ret} \quad \Delta H^{\ddagger}_{inv}}{RT} + \text{Const.}$$

If two reactions have the same reaction order, which was proved to be the case in Table 3 of the foregoing chapter, the ratio of the two rate constants, k_{ret} / k_{inv} , can be substituted for the ratio of two reaction products, (*threo*-II) / (*erythro*-II) . Therefore, a straight line should be obtained, if log((*threo*-II) / (*erythro*-II)) are plotted vs. 1/T, and the results are shown in Figure 2. From the results, $\Delta H^{\ddagger}_{ret} > \Delta H^{\ddagger}_{inv}$ and $\Delta S^{\ddagger}_{ret} > \Delta S^{\ddagger}_{inv}$ are obtained. The enthalpic factor favors the formation of the inverted product, while entropic one favors the

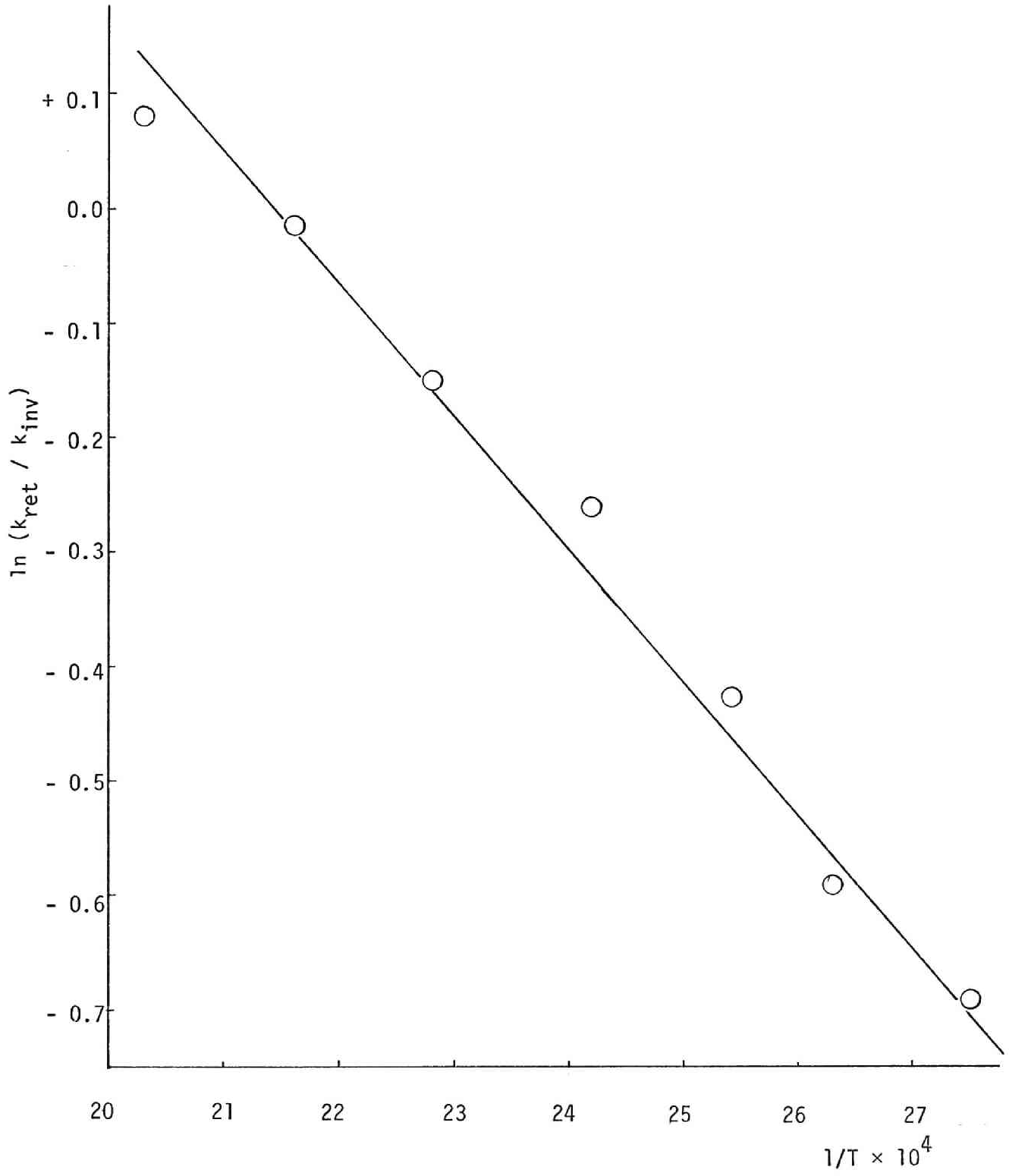


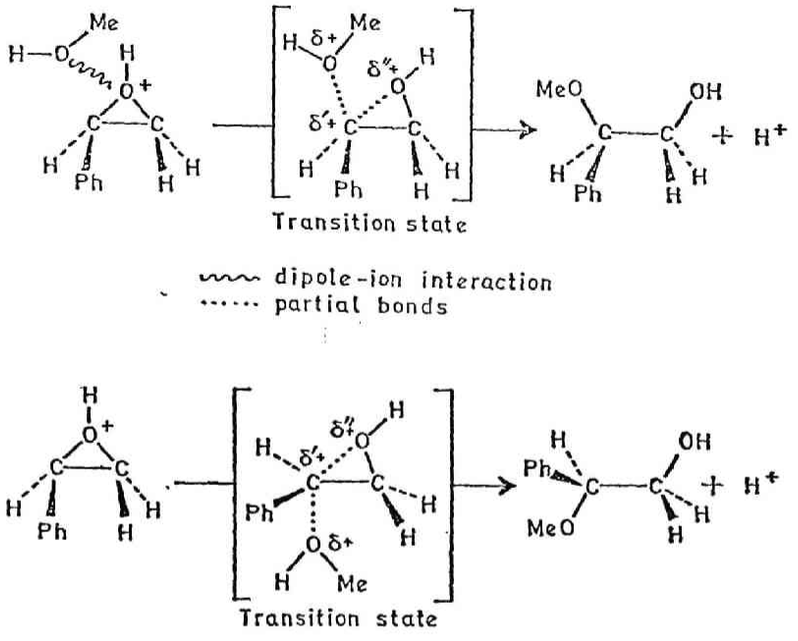
Fig. 2. Plot of $\ln(k_{ret} / k_{inv})$ vs. 1/T for the ethanolysis of *trans*-2,3-diphenyloxirane.

retention reaction.

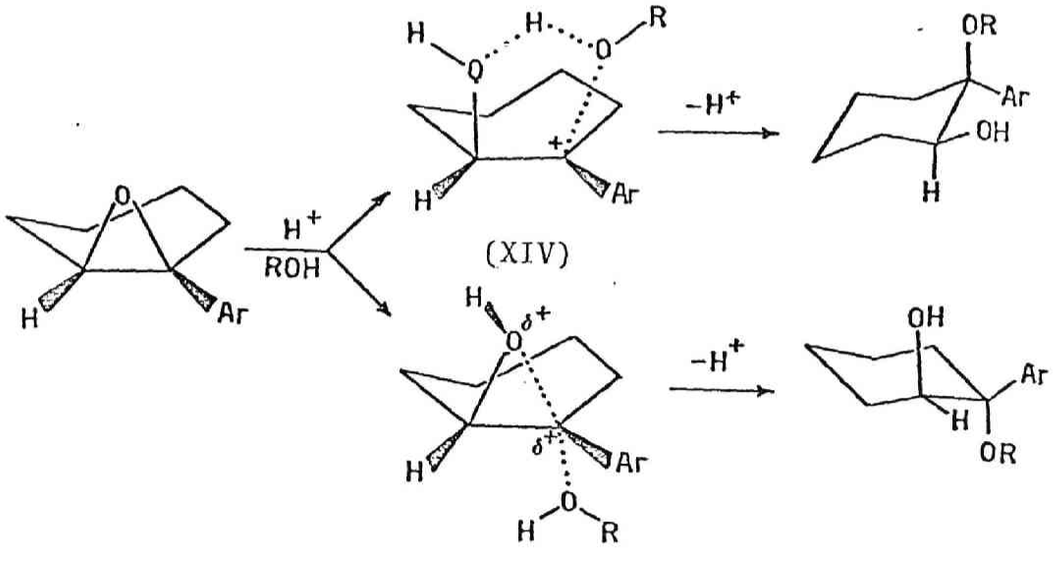
Macchia *et al.* proposed the mechanism shown in Scheme 2 for the acid-catalyzed solvolysis of 1-aryl-1,2-epoxycyclohexanes.[9] However, the author cannot agree with their mechanism on the basis of the following considerations; the entrophy of the transition state (XIV) is expected to be equall to, or to be smaller than that of (XV), because (XIV) involves a molecule of ethanol; and the enthalpy of (XIV) is expected to be smaller than that of (XV), because hydrogen bonding from the ethanol involved in the transition state to the oxygen of the epoxide supplys an additional stabilization energy to (XIV), which are contrary to the observations.

Bruice *et al.* examined the temperature effects on the product distributions of hydrolysis of phenanthrene 9,10-oxide,[15] and reported relative activation parameters; $\Delta H^{\ddagger}_{ret} - \Delta H^{\ddagger}_{inv} = 2.05$ kcal mol^{-1} and $\Delta S^{\ddagger}_{ret} - \Delta S^{\ddagger}_{inv} = 5.0$ cal deg^{-1} mol^{-1}. They explained their observations by an S_N1 mechanism. However, the energy difference 2.05 kcal mol^{-1} seems to be rather large for the fast reaction step after rate determining formation of a carbonium ion.

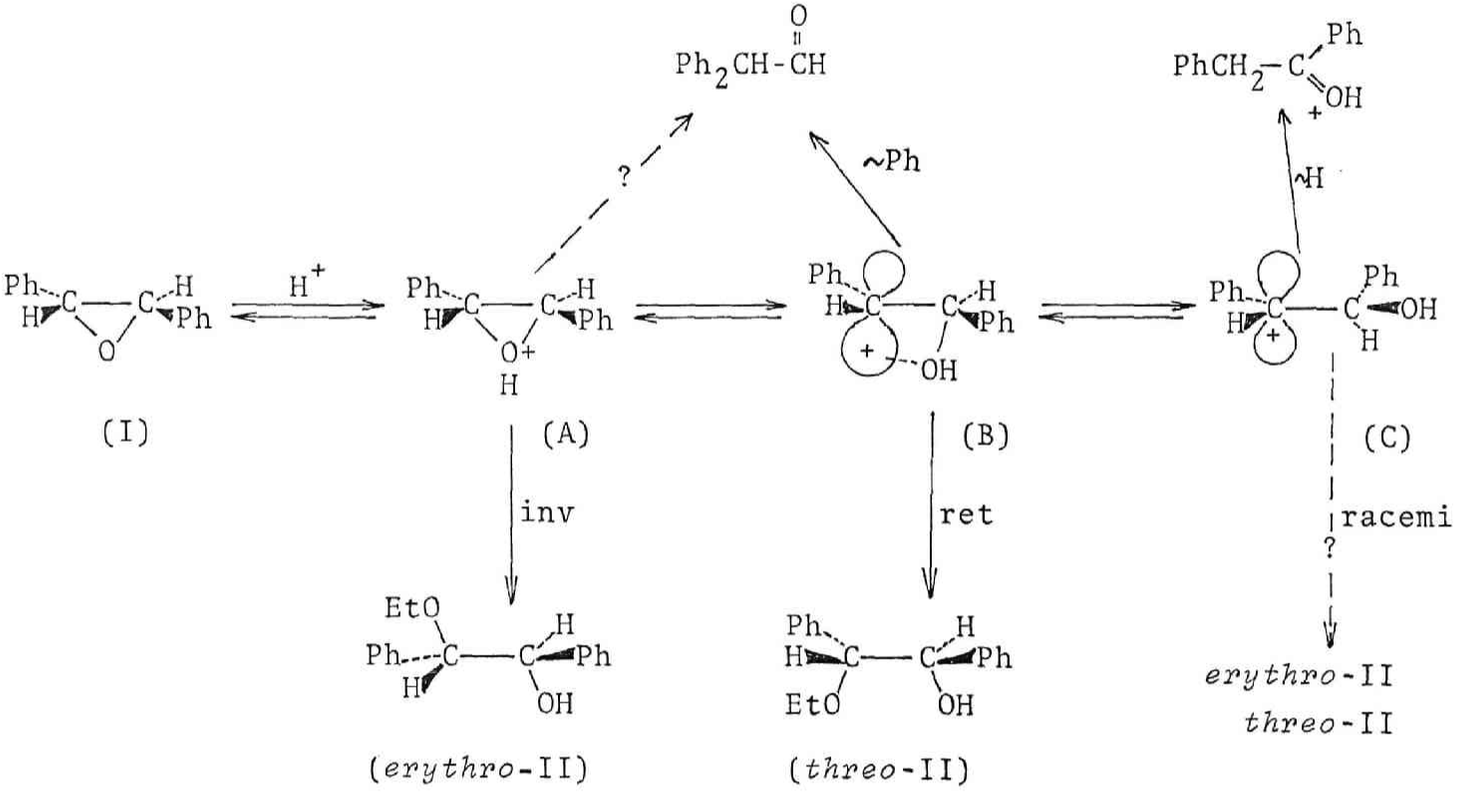
Possible mechanism for the reaction are shown in scheme 3 in which (A) is the conjugate acid of the epoxide and (C) is a completely developed carbonium ion. The intermediate (B) is considered to be in a circunstance in which p-orbital of the cation is solvated by intramolecular hydroxyl group.



Scheme 1



Scheme 2


Ph2CH-CH
O
?
~Ph
PhCH2-C
Ph
OH
~H
H+
(I)
(A)
(B)
(C)
inv
ret
racemi
?
EtO
OH
(erythro-II)
(threo-II)
erythro-II
threo-II

Scheme 3

As the broken C-O bond provides more freedom to the system, the reaction which yields retained product has lower activation entropy than the reaction yielding the inverted product.

3 Experimental

Materials and analytical methods have been described in the foregoing chapter.

Ethanolysis of (I) in an autoclave. To a 1 ml ethanolic solution containing 10 mg of (I), a definite volumn of hydrochloric acid solution in ethanol (0.005 mol/l) was added. The reaction mixture was shaken vigorously, set in an autoclave, and heated up to the desired temperature. Ten minutes usually and thirty minutes at the longest were required to arrive at the reaction temperature. After an appropriate time interval at that temperature, the mixture was cooled, poured into a sampling tube containing a small amount of potassium carbonate, and then treated as mentioned in the foregoing chapter.

References and Notes

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3) R. W. Taft, Jr., *J. Am. Chem. Soc.*, 74, 5374 (1952); R. W. Taft, Jr., E. L. Purlee, P. Riesz, and C. A. DeFazio, *ibid.*, 77, 1584 (1955).

4) Long *et al* themselves concluded from the results that ring-opening proceeds by an A1 mechanism.

5) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, 59, 737 (1959); Parker-Isaacs conclution was criticized again by Pritchard and Siddiqui, J. G. Pritchard and I. A. Siddiqui, *J. Chem. Soc., Perkin II*, 1973, 452.

6) Chapter I of this thesis.

7) J. Biggs, N. S. Chapman, A. F. Finch, and V. Wray, *J. Chem. Soc., (B)*, 1971, 55; J. Biggs, N. B. Chapman, and V. Wray, *ibid.*, 1971, 71.

8) F. Fisher and H. Koch, *Chem. Ber.*, 99, 2000 (1966).

9) C. Battistini, P. Crotti, and F. Macchia, *Tetrahedron Lett.*, 1975, 2091.

10) In this chapter, the same numbers are assigned to all the compounds as those in the foregoing chapter.

11) H. O. House, *J. Am. Chem. Soc.*, 77, 3070 (1955).

12) D. L. Whalen, A. M. Ross, P. M. Dansette, and D. M. Jerina, *J. Am. Chem. Soc.*, 99, 5672 (1977).

13) G. Lamaty, R. Maleq, C. Selve, A. Sivade, and J. Wylde., *J. Chem. Soc., Perkin II*, 1975, 1119.

14) Vapor pressure of ethanol at 230 °C is 50 atom. Pressure effects on the reaction kinetics are ignored, since they are rather small at the range of pressure of these experiments.

15) P. Y. Bruice, T. C. Bruice, P. M. Dansette, H. G. Selander, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, 98, 2966 (1976).

CHAPTER VII Co-solvent Effects on the Stereochemistry of Acid-Catalyzed Hydrolysis of *trans*-2,3-Diphenyloxirane

Acid-catalyzed hydrolysis of *trans*-2,3-diphenyloxirane was examined in binary aqueous mixtures containing various kinds of co-solvents. When highly polar and weakly basic co-solvents such as acetonitrile and sulfolane were used, the reaction yields large amounts of retained 1,2-diphenyl-1,2-ethanediol, while solvent systems containing DMSO and HMPA which have high polarities and strong basicities afforded large amounts of inverted product. Moderately basic ethereal co-solvents had slightly inversive effects on the reaction. The co-solvent effects can be explained in terms of solvation shell concept outlined in previous chapter. Stereochemistry of hydrolysis of the title compound in pure water was estimated in the range from 70% retention-30% inversion to 60% retention-40% inversion.

1 Introduction

With the recent demonstration that arene oxides function as the initial intermediates in the enzymatic formation of phenols and other metabolites of the aromatic nucleus,

considerable interest has developed in the chemical and biological fate of these labile compounds.[1] In paticular, arene oxides have been implicated as agents in the toxicity, mutagenicity, and carcinogenicity of mono- and polycyclo aromatics.

Those hydrocarbons that exhibit carcinogenic activity have a common structural feature called a K-region whose excision from the aromatic hydrocarbon leaves only cyclic cojugated aromatic rings; thus the 9-10 bond of phenanthrene is a K-region. Because of the association of carcinogenic activity with the presence of a K-region, the reaction mechanisms by which K-region arene oxides isomerize to phenols and react with nucleophiles are particurally interested in.[2]

To understand the specific reactivity of K-region arene oxides, knowledge should be accumulate on the reactivity of diaryloxiranes. Following chapter V which dealt with ethanolysis of *trans*-2,3-diphenyloxirane (I), this chapter reports experimental results of hydrolysis of I in binary aqueous mixtures, and discusses the mechanism of the reaction and co-solvent effects on the stereochemistry of the reaction.

2 Results and Discussion

Experiments were carried out in similar ways as those of ethanolysis in binary ethanolic mixtures. As the product 1,2-diphenyl-1,2-ethanediols (II) are unstable under

GC analysis conditions, the crude products were column-chlomatographed, and the distributions of two stereoisomers in isolated II were determined from the intensity integral of the methine protons on NMR spectra. As the accuracy of integral is rather low, the results may involve 5% error at highest. Results are shown in Figs. 1-7.

As I is slightly soluble in water, the colloidial precipitates of I were dispersed when large amounts of water were added to solutions of I in co-solvent except THF. The experiments which were carried out by addition of acid-solution to the dispersed systems are shown by a mark ●, while homogeneous reactions are shown by a mark ○ in Figs. 1-7. Experiments could not be carried out in the high water proportion region of aqueous THF system because of the separation of THF solution layer of I.

When the plots of experimental results in the figures are extrapolated to the points of pure water, all of the values obtained in various solvent systems are in the range from 70% retention-30% inversion to 60% retention-40% inversion, which could be considered to be the stereochemical result of hydrolysis of I in pure water. The selectivity of the retained product of hydrolysis of I in pure water is lower than that of acetolysis in pure acetic acid[3] and yet greater than that of ethanolysis in pure ethanol.

Most probable reaction routes to the products of acid-catalyzed solvolysis of I are shown in scheme 1, which has

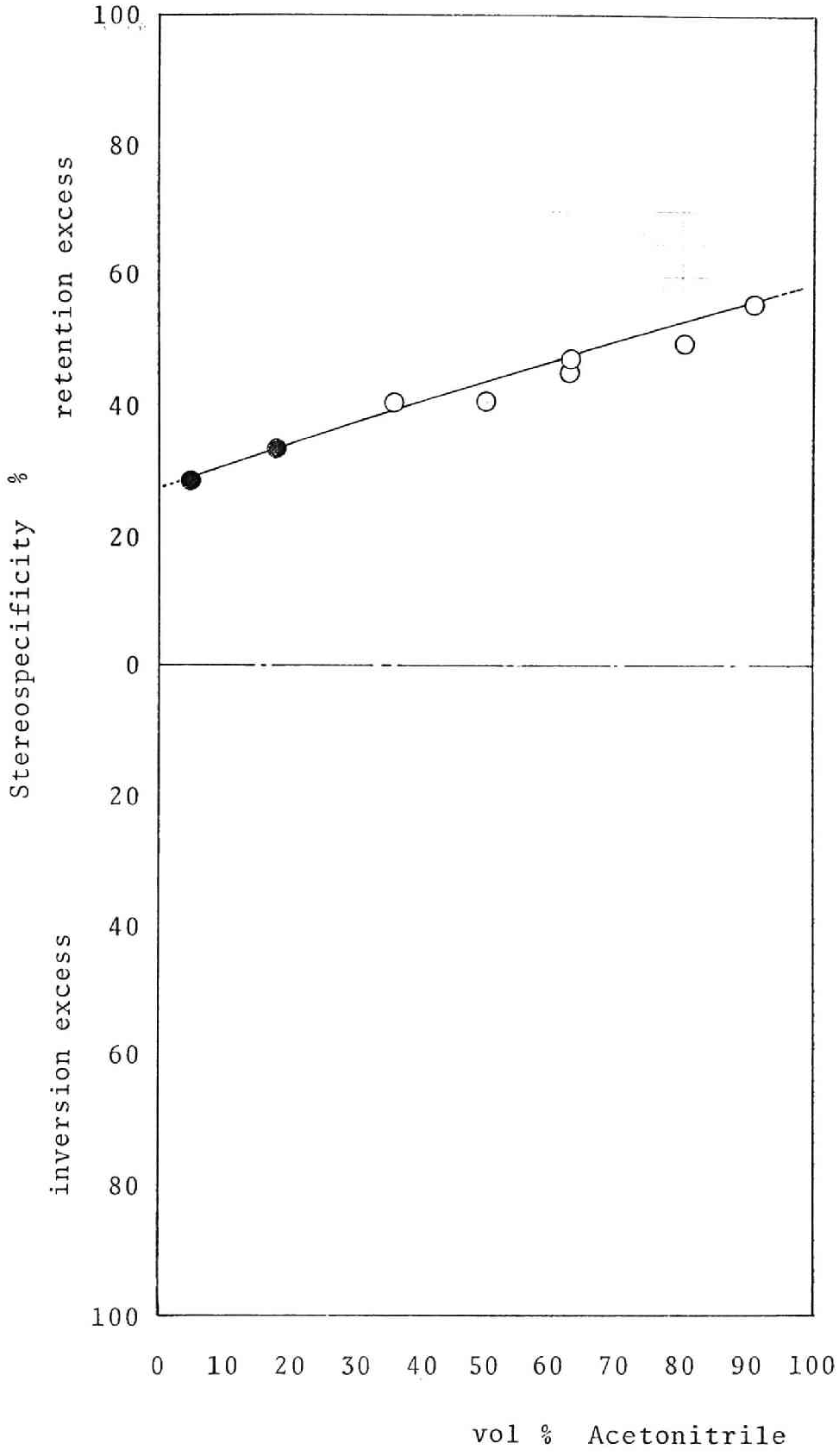


Fig. 1. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxirane in aqueous acetonitrile at 50 °C.

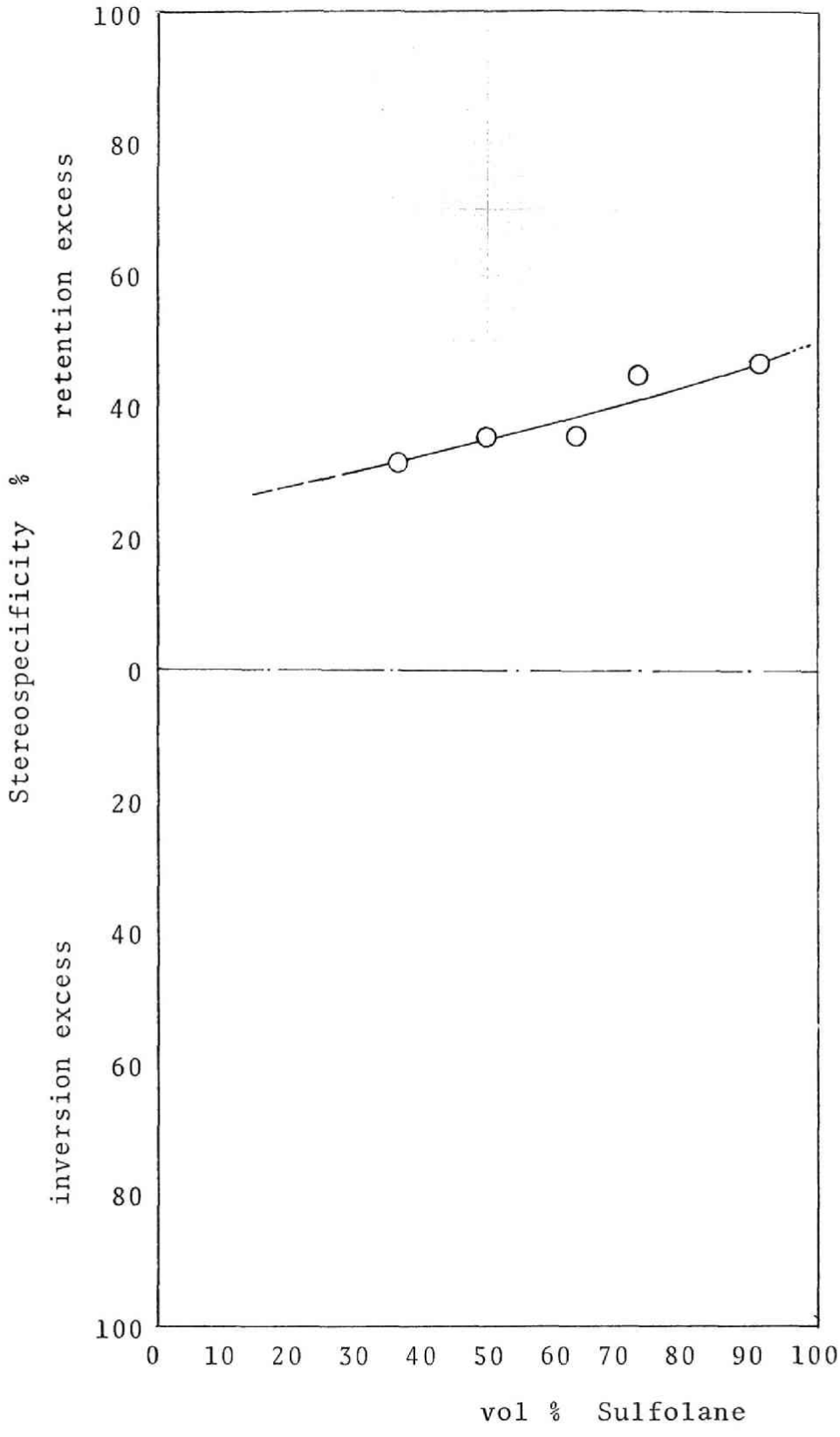


Fig. 2. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxirane in aqueous sulfolane at 50 °C.

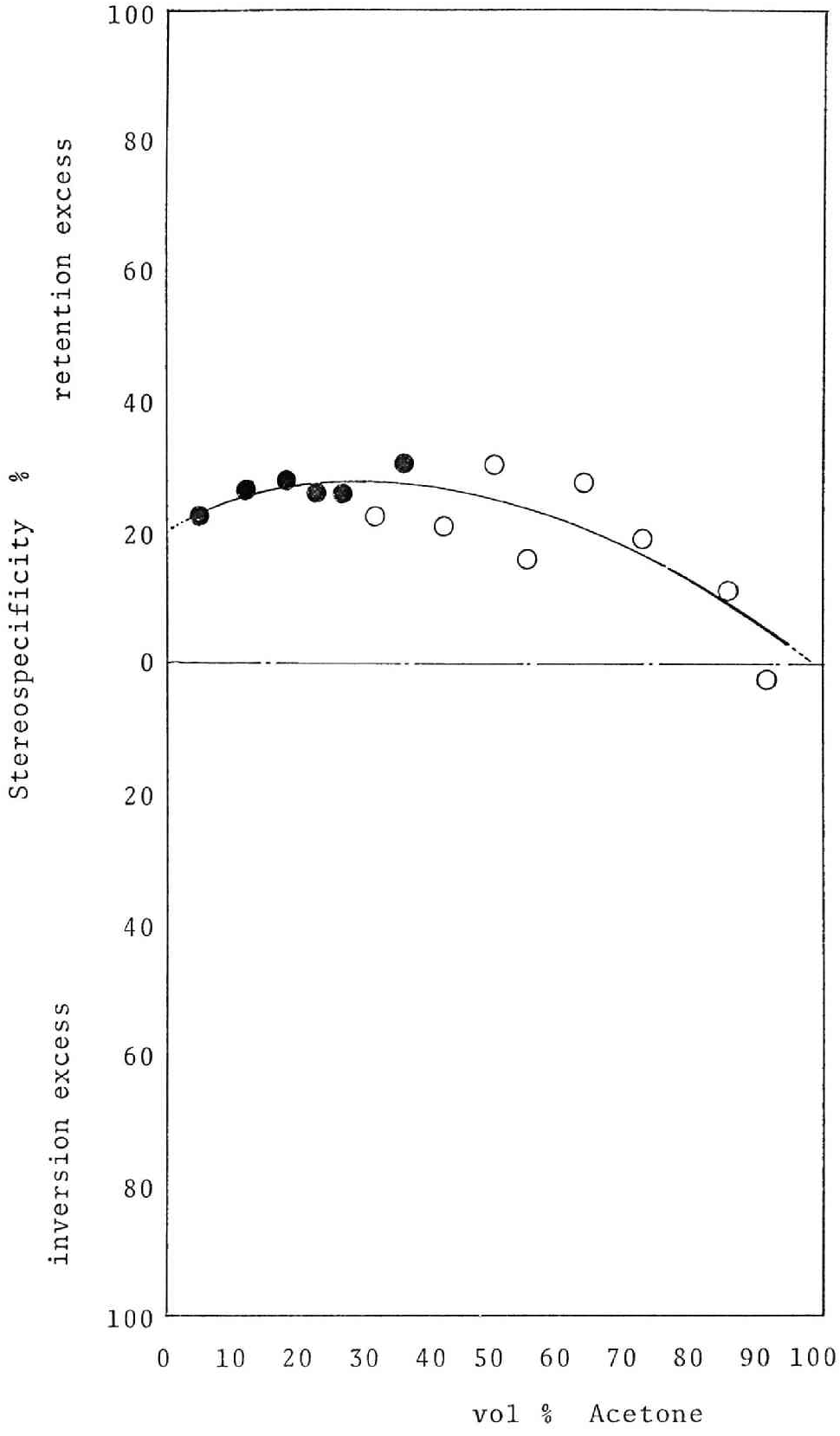


Fig. 3. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxirane in aqueous acetone at 50 °C.

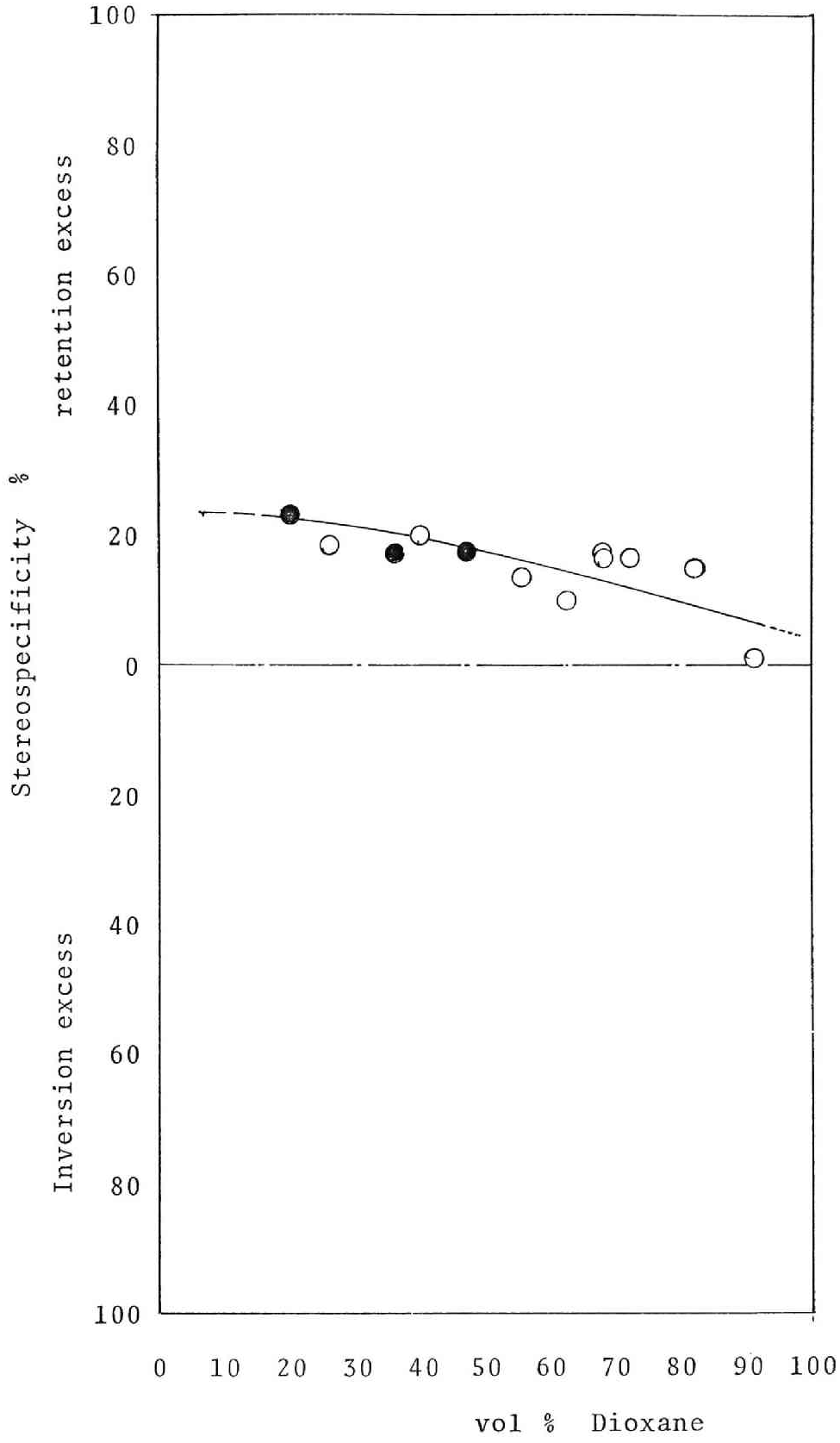


Fig. 4. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxirane in aqueous dioxane at 50 °C.

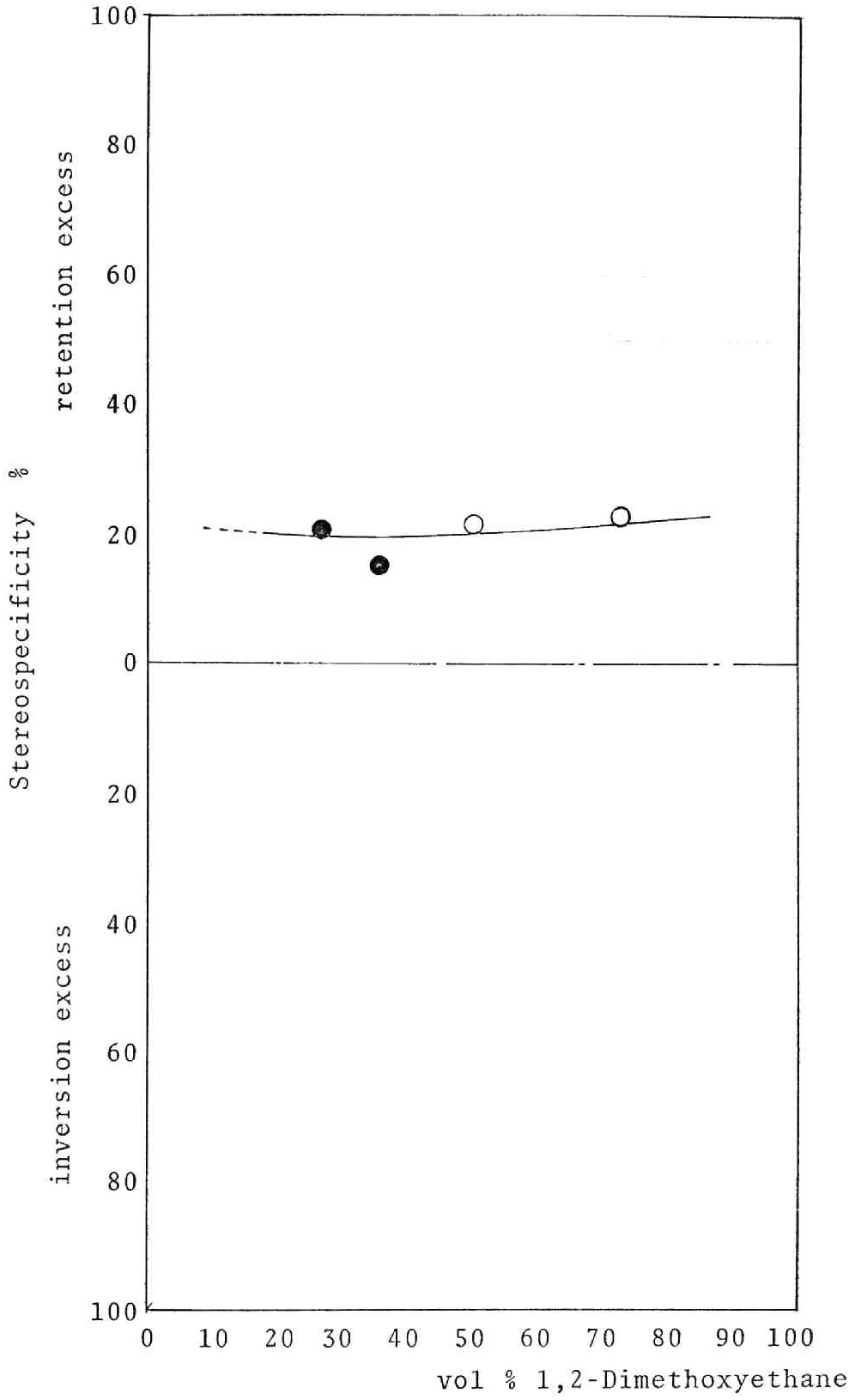


Fig. 5. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxane in aqueous 1,2-dimethoxyethane at 50 °C.

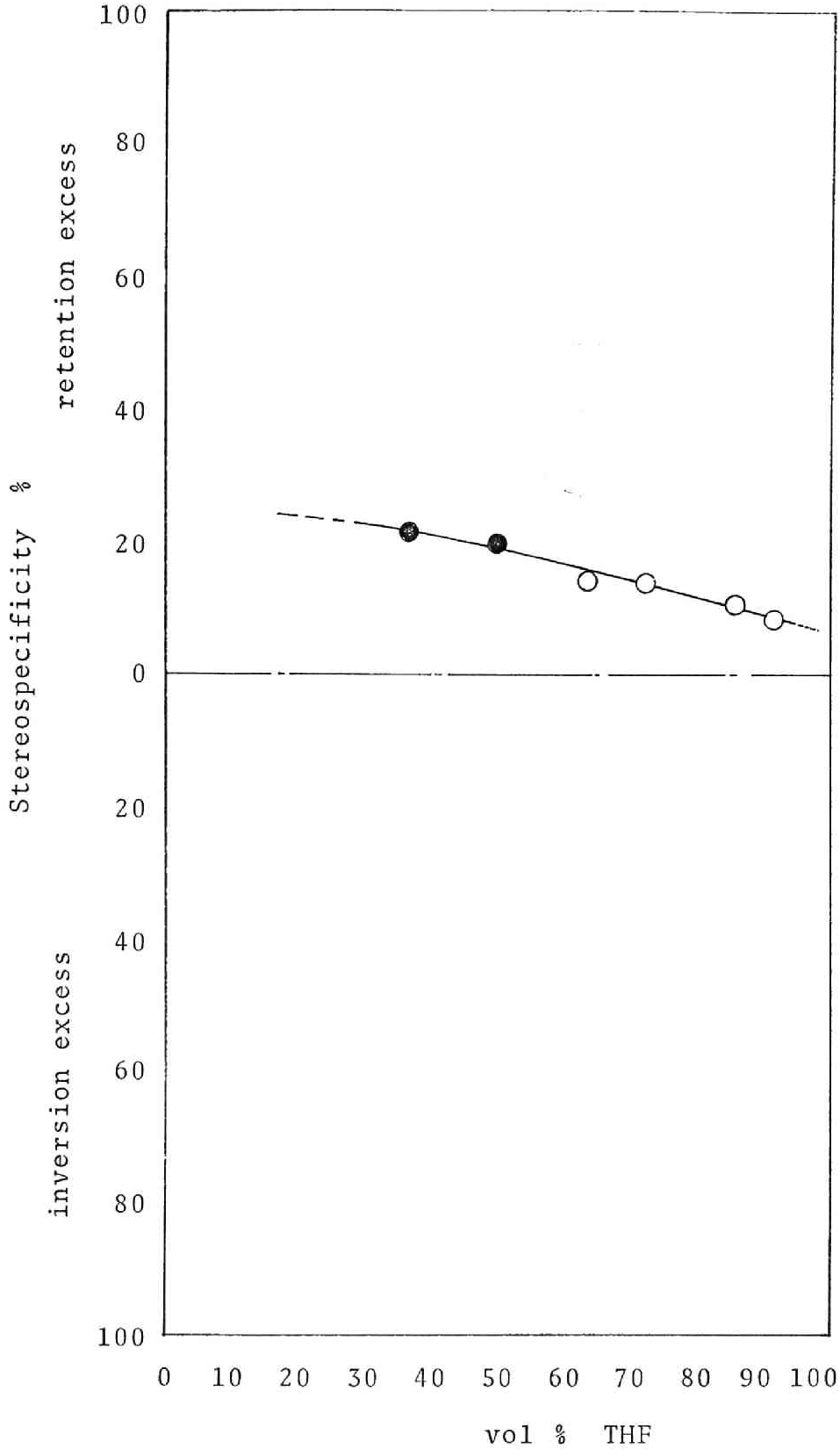


Fig. 6. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxirane in aqueous THF at 50 °C.

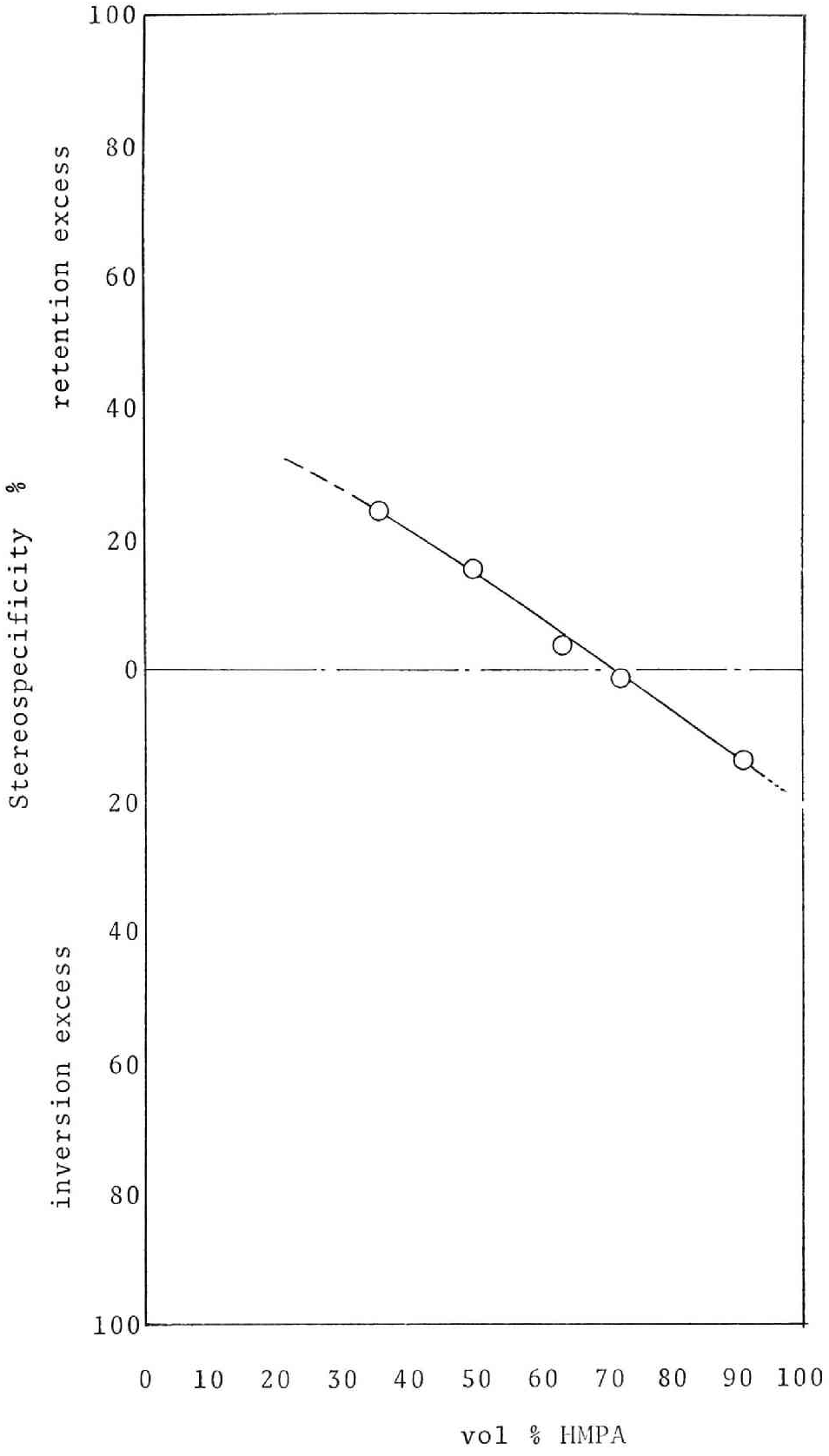
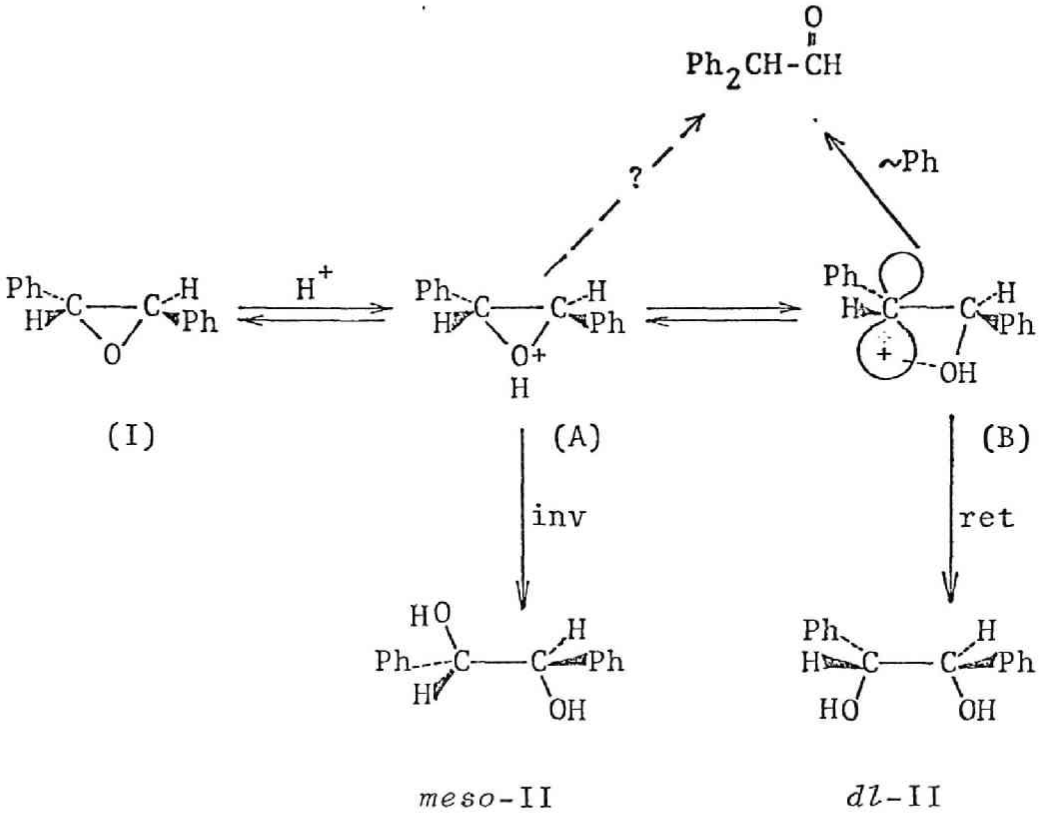


Fig. 7. Stereospecificity of the hydrolysis of *trans*-2,3-diphenyloxirane in aqueous HMPA at 50 °C.

been discussed in the foregoing chapter. When basicities of oxygens in ethanol, water, and acetic acid are taken into account, which will be discussed in the latter part of this chapter, nucleophilicities of these protic solvents decrease in the following order:[4] $CH_3CH_2OH > H_2O > CH_3CO_2H$. As the reaction paths from (A) to inverted products are affected by the nucleophilicities of the solvents, the reaction rates of these reaction paths decrease in the above order. On the other hand, the reaction paths from (B) to retained products are less affected by the nucleophilicities because of the carbonium ion character of the intermediate (B). Therefore, the selectivities of the retained products decrease in the order of the reaction mentioned above.

Solvent effect on the equilibrium between (A) and (B) is a delicate problem, but is expected to be small since both (A) and (B) are charged species. The cation (B) which is in higher energy level than (A) is expected, however, to be more stabilized in highly polarized solvents, which also favors the formation of the retained product in water.

Ito reported that the dielectric constant of co-solvent is an important facter affecting the stereochemistry of hydrolysis of I.[5] However, his proporsal cannot explain the following observations; I gives large amounts of the retained product in solvent systems containing acetonitrile (ε = 37.5) or sulfolane (ε = 43.3), while solvent systems,



Scheme 1

H_2O-DMSO (ε = 46.68) and H_2O-DMF (ε = 36.71) afford large amounts of the inverted product.

In the previous chapter, the author has discussed the co-solvent effects on ethanolysis of I, and concluded that basicity as well as polarity is an important factor affecting the stereochemistry of the reaction. The results of hydrolysis can be explained in the same ways as those of ethanolysis. The co-solvent effects on ethanolysis and hydrolysis are summerized in Table 1. The difference between the results of the two reactions is that group 2 co-solvents have slightly retentive effects on ethanolysis, while they have inversive effects on hydrolysis, although the results of only a few ethers of group 2 are available for the co-solvent of hydrolysis.

Many workers have challenged to determine the basicity of water, but reported pKa values of hydronium ion H_3O^+ are diverse in a wide range of; -10.1,[6] -6.66,[7] -5.1,[8] -3.43,[9] -2.35,[10] -1.8,[11] and 1.6.[12] Inductive effects of ethyl group, however, appears to cause ethanol to have more basic character than water, which is comfirmed by affinity to proton in gas phase.[13]

If basicities of ethereal co-solvents of group 2 are weaker than that of ethanol and stronger than that of water,[14] co-solvent effects on solvolysis mentioned in Table 1 can be explained in terms of the solvation shell concept as follows. In the binary solvent systems, stereochemistry of solvolysis

Table 1. Co-solvent Effects on the Stereochemistry of Solvolysis of I.

Group	Basicity	Dielectric polarizability	Typical solvents	Stereochemistry	
				Ethanolysis	Hydrolysis
1	weak	high	CH_3CN, Sulfolane	retentive	retentive
2	weak	low	Dioxane, (Benzene)	slightly retentive	slightly inversive
3	strong	high	DMSO, HMPA	inversive	inversive

of I is determined by effective concentrations of nucleophiles in regions A and B. As the basicity of water is weaker than that of group 2 co-solvents, effective concentration of water in region A decreases with an increasing proportion of co-solvent in medium, as compared with that in region B, and stereochemical outcome becomes more inversive. On the other hand effective concentration of ethanol in region A is not so much affected by addition of group 2 co-solvents to medium, while effective concentration of ethanol in region B decreases with an increase of co-solvent proportion, because ethanol is more basic than co-solvent. Therefore effects of group 2 co-solvents on ethanolysis are slightly retentive.

The stereochemical results of hydrolysis in binary mixtures containing group 1 and group 3 co-solvents can be explained in the completely same manner as those of ethanolysis.

Recently reaction mechanisms of hydrolysis of K region arene oxide have been investigated actively by means of kinetical study, and sometimes product distributions have been discussed. However, co-solvent effects on the product distributions are completely ignored, although hydrolysis experiments are always carried out in binary aqueous mixtures. The results described in this chapter suggest the importance of co-solvent effects on the stereochemistry of hydrolysis of K region arene oxide.

3 Experimental

Materials have been described in chapter V. NMR spectra were recorded on a JEOL PMX-60 spectrometer.

Typical Experiment Procedure. To a solution of I (100 mg) in acetonitrile (14 ml) and water (6 ml) held in a controlled-temperature block, 2 ml of 0.1 N sulfuric acid solution was added with vigorous shaking. The reaction mixture was allowed to stand for 4 h at 50.0 ± 0.05 °C. Then a small amount of potassium carbonate was added with shaking, and the mixture was cooled. Acetonitrile was removed on a rotary evaporator, and residual aqueous layer was extracted with 20 ml of ether four times. Combined ether layers were dried over sodium sulfate. After removal of the solvent, dried product was chromatographed on 8ϕ × 200 mmH silica gel column. Benzene (50 ml) eluted 54.1 mg of the rearranged products which were composed of 60% bezophenone and 40% diphenylacetaldehyde accompanied with a small portion of 1,2-diphenylethanol. Then ether eluted 74.5 g (68.2%) of 1,2-diphenyl-1,2-ethanediols. NMR analysis showed that the product was composed of 27.4% *meso*-isomer and 72.6% *dl*-isomer. No other product was found in the NMR spectrum.

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1) T. C. Bruice and P. Y. Bruice, *Acc. Chem. Res.*, 9, 378 (1976); D. M. Jerina and J. W. Daly, *Science*, 185, 573 (1974).

2) P. Y. Bruice, T. C. Bruice, P. M. Dansette, H. G. Selander, H. Yagi, and D. M. Jerina, *J. Am. Chem. Soc.*, 98, 2965 (1976); P. Y. Bruice, T. C. Bruice, H. Yagi, and D. M. Jerina, *ibid*, 98, 2973 (1976); J. W. Keller and C. Heidelberger, *ibid*, 98, 2328 (1976); D. L. Whalen, A. M. Ross, P. M. Dansette, and D. M. Jerina, *ibid*, 99, 5672 (1977); see also, G. H. Posner and D. Z. Rogers, *ibid*, 99, 8214 (1977).

3) Acid-catalyzed acetolysis of I followed by hydrolysis with alkali afforded more than 80% retained glycol II, Y. Taguchi, private communication.

4) Solvolysis of *n*-butyl bromide (S_N2) in water proceeds 2.1 times faster than in ethanol at 75.1 °C,[4a] and one may consider that water is more nucleophilic than ethanol. However, the result should be attributed to the increased stability (solubility) of the hydrophobic solute in ethanol as compared with in water.[4b]

4a) M. L. Bird, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1943, 255.

4b) M. J. Blandamer and J. Burgess, *Chem. Soc. Rev.*, 4, 55 (1975).

5) S. Ito and N. Nonura, *Nippon Kagaku Kaishi*, 1972, 1985.

6) R. J. Gillespie and C. Solomons, *J. Chem. Soc.*, 1957, 1796.

7) N. C. Deno and R. W. Taft, Jr., *J. Am. Chem. Soc.*, 76, 244 (1954).

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9) L. P. Hammett and A. J. Deyrup, *J. Am. Chem. Soc.*, 54, 4239 (1932).

10) H. Lemaire and H. J. Lucas, *J. Am. Chem. Soc.*, 73, 5198 (1951).

11) J. N. Bronsted and W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, 25, 59, (1929).

12) A. J. Deyrup, *J. Am. Chem. Soc.*, 56, 60 (1934).

13) J. F. Wolf, R. H. Staley, I. Koppel, M. Taagepera, R. T. Mclver, Jr., J. L. Beauchamp, and R. W. Taft, *J. Am. Chem. Soc.*, 99, 5417 (1977).

14) Base strength was reported as; BuOH > Bu_2O > H_2O at the temperature range from 1 °C to 50 °C, W. Gerraed and E. D. Macklen, *Chem. Rev.*, 59, 1105 (1959).

CHAPTER VIII Acid-Catalyzed Solvolysis of *trans*-2,3-Diphenyloxirane in Binary Solvent Mixtures of Ethanol and Water

The stereochemistry of the title reaction was examined in various composition of solvents at 70 °C. With increasing proportions of water in the medium, the proportions of the retained products in both 1,2-diphenyl-1,2-ethanediols and 2-ethoxy-1,2-diphenylethanols increased. The results can be explained by the reaction mechanism proposed in the previous chapters.

1 Introduction

The author has discussed the reaction mechanism of acid-catalyzed solvolysis of *trans*-2,3-diphenyloxirane (I) and also the co-solvent effects on the stereochemistry of ethanolysis and hydrolysis of the same compound in chapters V and VII, respectively. As protic solvents have not been dealt with as co-solvents in these chapters, a solvent system composed of water and ethanol should be examined, since water is regarded as a co-solvent of ethanolysis and ethanol is regarded as a co-solvent of hydrolysis. This chapter reports the effects of the solvent composition of water-ethanol system on the stereochemistry of solvolysis of (I), and reexamines the mechanism of the reaction.

2 Results and Discussion

Reactions were carried out in a similar way as those of chapters V and VII. The reaction yields 1,2-diphenyl-1,2-ethanediols (II), 2-ethoxy-1,2-diphenylethanols (III) and the rearrenged products (diphenylacetaldehyde (IV), diethyl acetal of IV (V), and benzophenone (VI), an oxidazed product of IV. After the usual work-up, crude products were column-chromatographed to separate the components. The stereo-isomeric distributions were determined by intensity integrals of methine protons of II, and by relative area ratios of *threo*- and *erythro*-III on gas chromatogram. Results are shown in Fig. 1. The proportion of the retained products in both II and III increased with increasing proportions of water in the media. As ethanol is more basic than water[1] and water is more polar than ethanol, the results may be predicted by the solvation shell concept as follows: Water in the medium should have the same effects on ethanolysis as acetonitrile which is a weaker base than ethanol, and ethanol in the medium should have the same effects on hydrolysis as HMPA which is a stronger base than water; then water should have retentive effects on ethanolysis and ethanol should have inversive effects on hydrolysis. However, this prediction is oversimplified, because both water and ethanol have stronger nucleophilicity as compared with the co-solvents described in the previous chapters.

As was mentioned in chapter VI, the most probable

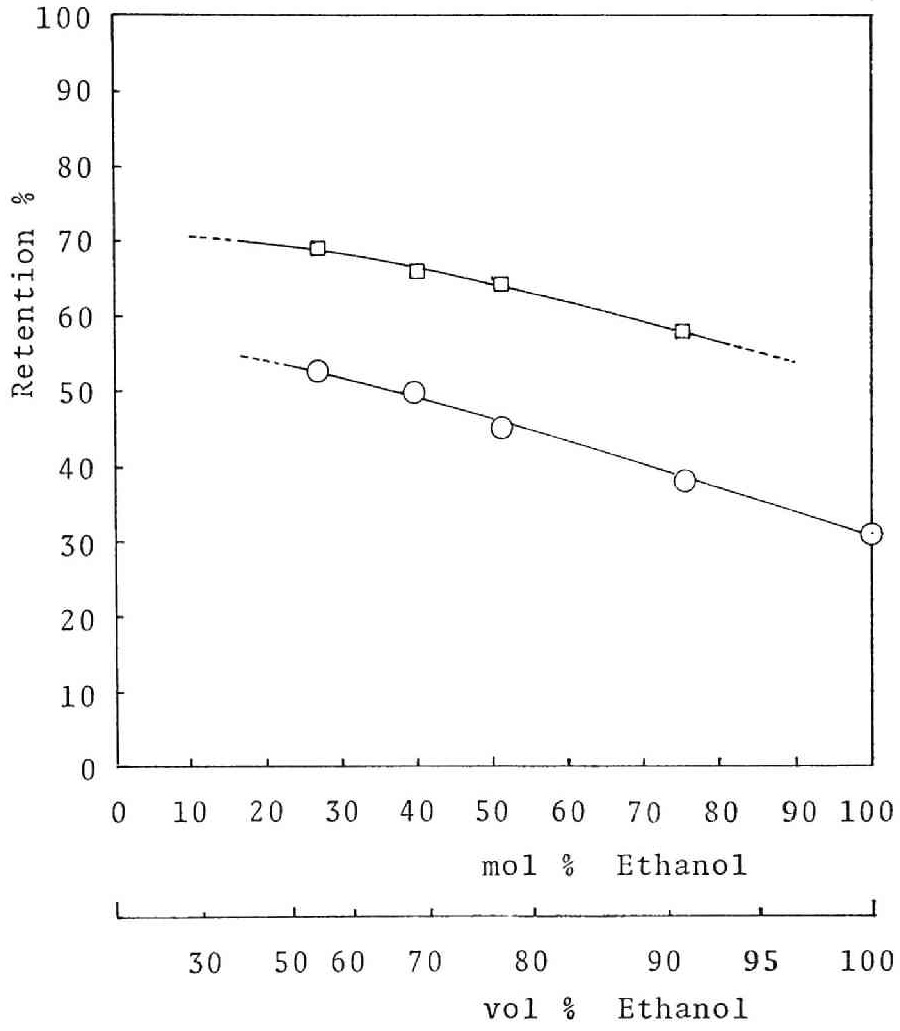
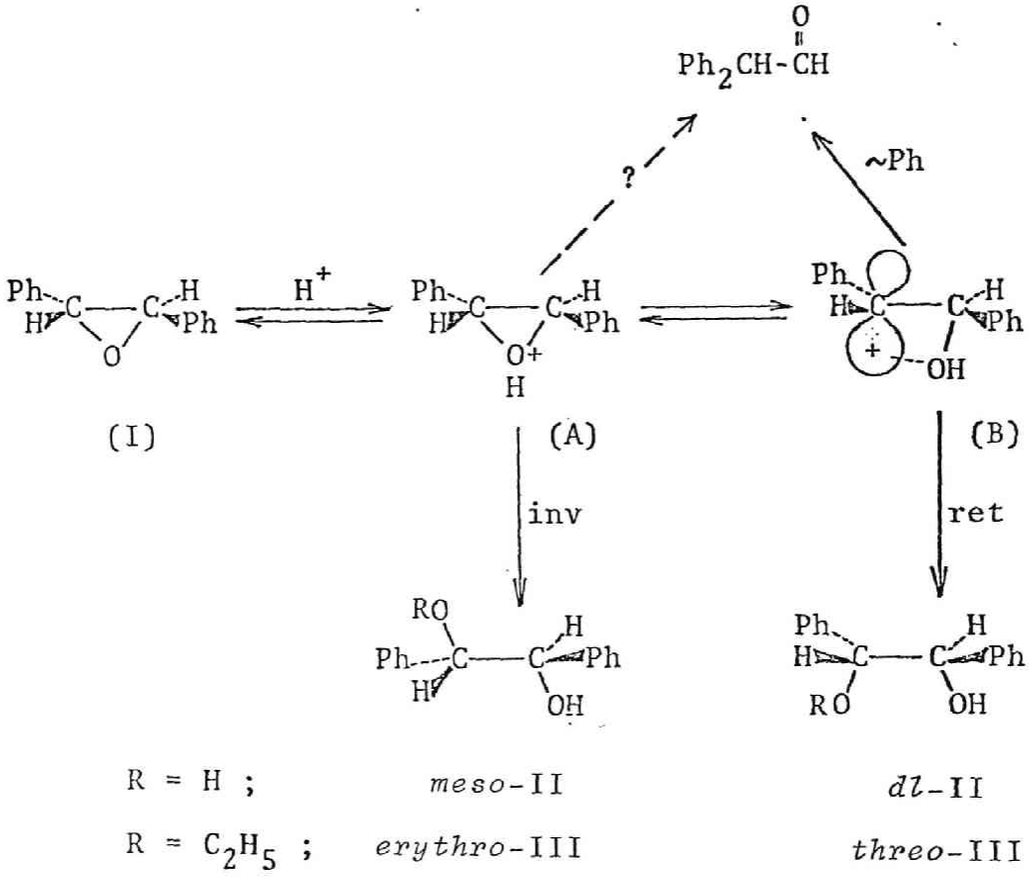


Fig. 1. Stereoisomeric distributions of the products of solvolysis of I in aqueous ethanol at 70.0 °C.

□; 1,2-diphenyl-1,2-ethanediol

○; 2-ethoxy-1,2-diphenylethanol


Ph2CH-CH
O
?
~Ph
H+
(I)
(A)
(B)
inv
ret
RO
OH
R = H ;
R = C2H5 ;
meso-II
erythro-III
dl-II
threo-III

Scheme 1

mechanism of solvolysis of I is shown in scheme 1. As both inverted II and III are considered to come from the intermediate (A), product distributions in the inverted products should be examined. As both retained II and III are considered to come from the intermediate (B), the product distibutions in retained products are important for the mechaistic considerations. Figure 2 shows the changes in product distributions in both retained and inverted products with the variations of the composition of solvents. Obviously, the inversion reaction favored the formation of III, while the retention reaction favored that of II. It is interesting to compare the results with those reported by Ingold *et al.*.[2,3] They examined the effects of the composition of ethanol-water solvent system on the product distribution of solvolysis of *n*-butyl bromide and *tert*-butyl chloride. As is shown in Fig. 3, *n*-butyl bromide favor the reaction with ethanol as compared with *tert*-butyl chloride. It is generally accepted that solvolysis of *tert*-butyl chloride obeys unimolecular mechanism, and that solvolysis of *n*-butyl bromide is caused by nucleophilic attack of solvent molecules on carbon.[4] Therefore, their observations are reasonably explained by the following considerations; *n*-butyl bromide yields larger amounts of ethereal product because of higher nucleophilicity of ethanol than water, and carbonium ion formed from *tert*-butyl chloride does not choose solvent molecules.

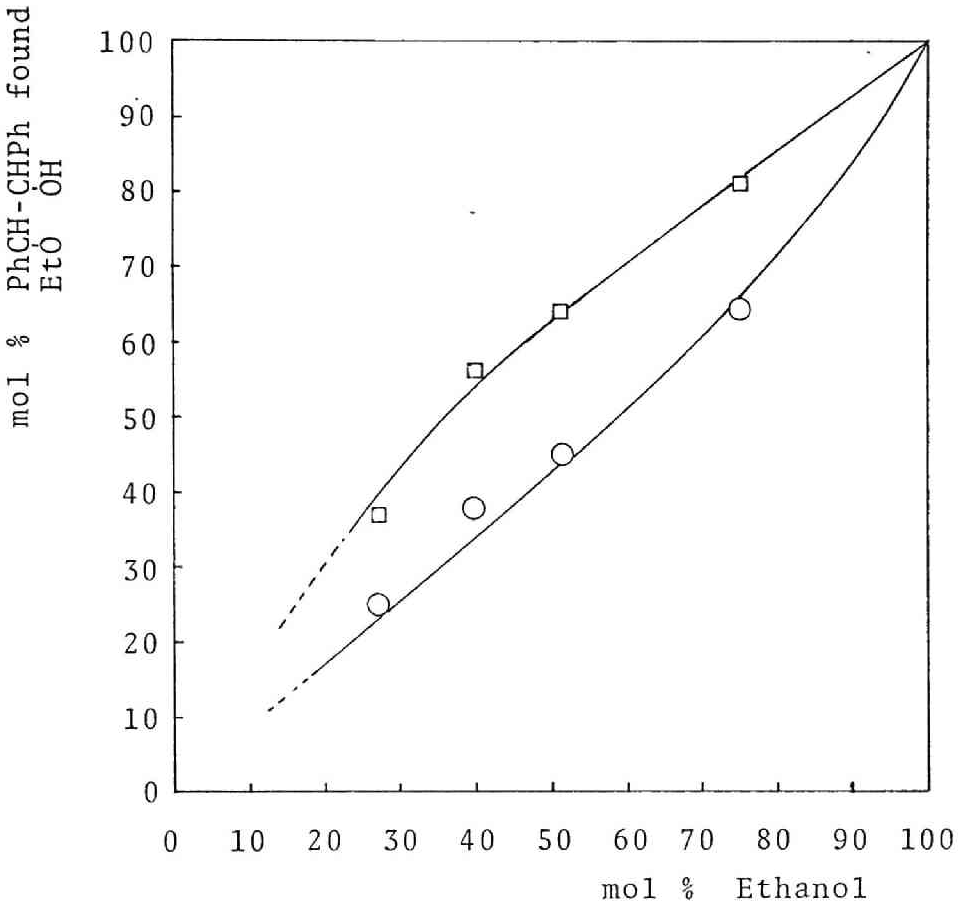


Fig. 2. Product distribution in retained and inverted products of solvolysis of I in aqueous ethanol at 70 °C.

□; Inverted product (through A)

○; Retained product (through B).

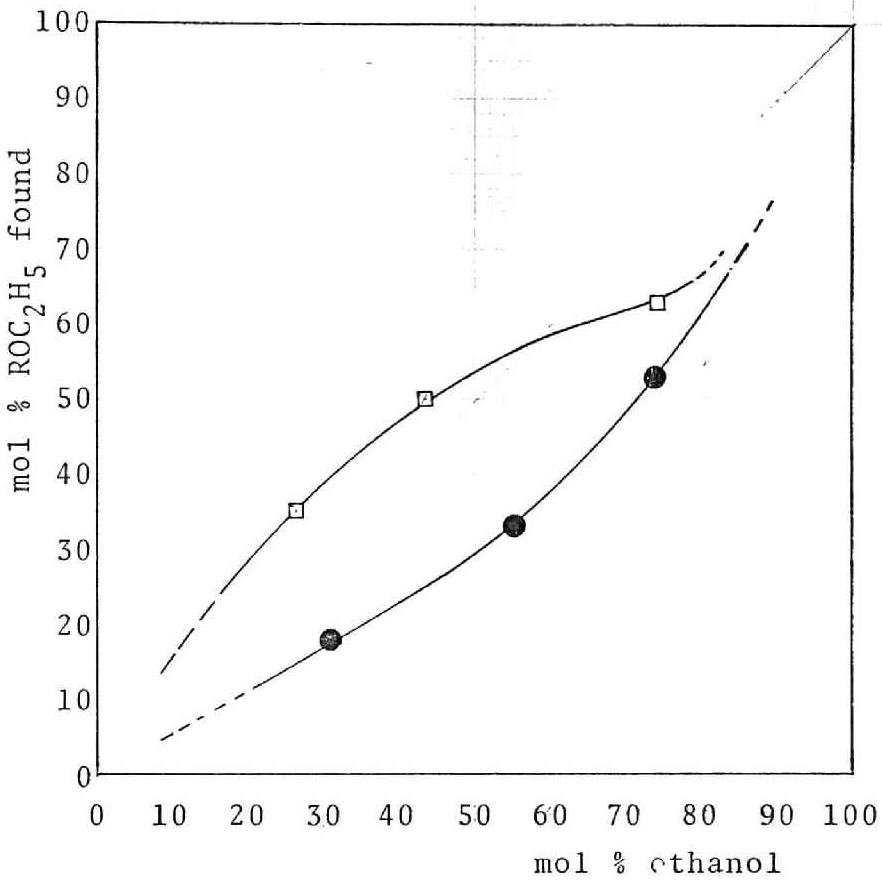


Fig. 3. Solvolysis in aqueous ethanol.

□: *n*-Butyl bromide at 75.1 °C.

●: *tret*-Butyl chloride at 25.0 °C.

L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1938, 881; M. L. Bird, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1943, 255.

Similarly, the results in Fig. 2 can be explained by scheme 1. As solvent molecules attack the intermediate (A) *via* an S_N2 mechanism to yield inverted product, ethereal product (III) is favored by the reaction. As the intermediate (B) has a carbonium ion character, (B) does not select the solvent molecules or (B) may favor the reaction with water, since the transition state from (B) to the retained II, as compared with the case of III, is more stabilized by hydrogen bonding to oxygen (B) with the more acidic hydrogen of water than that of ethanol.

3 Experimental

Materials and experimental procedure have been described in chapters V and VII, respectively. In this section only column chromatographic separation of the product will be described. Dried product obtained by the usual work-up mentioned in chapter VII was column chromatographed on 8 mmϕ × 650 mmH silica gel column under 1 m head of elutant (hexane, hexane-benzene, and benzene-ethyl ether successively with concentration gradients). The products were eluted in the following order; (2-ethoxy-1,2-diphenylethanol), (*trans*-2,3-diphenyloxirane), (1,2-diphenylethanedione), benzophenone, (diphenylacetaldehyde), (benzyl phenyl ketone), 1,1-diethoxy-2,2-diphenylethane, (2-hydroxy-1,2-diphenylethanone), (1,2-diphenylethanol), *threo*-2-ethoxy-1,2-diphenylethanol, *erythro*-isomer, (2,2-diphenylethanol), *meso*-1,2-diphenyl-1,2-ethanediol, and *dl*-isomer. Products in parentheses were not formed in experiments of this chapter.

References and Note

1) See chapter VII of this thesis.

2) L. C. Bateman, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1938, 881; M. L. Bird, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 1943, 255.

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4) Dafforn and Streitwieser concluded that simple primary substrates react by an S_N2 mechanism, even when solvolyzed in solvents of very low nucleophilicity, e.g., trifluoroacetic acid or trifluoroethanol; G. A. Dafforn and A. Streitwieser, Jr., *Tetrahedron Lett.* 1970, 3159.

LIST OF PUBLICATION

CHAPTER I	*Bull. Chem. Soc. Jpn.*, 49, 1063 (1976).
CHAPTER II	*Bull. Chem. Soc. Jpn.*, 49, 1063 (1976).
CHAPTER III	*Bull. Chem. Soc. Jpn.*, 51, 174 (1978).
CHAPTER IV	*Nippon Kagaku Kaishi*, in press.
CHAPTER V	submitted for publication to *Bull. Chem. Soc. Jpn.*, partial report was presented at the 8th Meeting of "Tyubu Kagaku Kankei Kyokai Shibu Rengo," Nagoya, October 1977.
CHAPTER VI	to be published in *Bull. Chem. Soc. Jpn.*; partial report was presented at the 8th Meeting of "Tyubu Kagaku Kankei Kyokai Shibu Rengo," Nagoya, October 1977.
CHAPTER VII	to be published in *Bull. Chem. Soc. Jpn.*; partial report will apear at the 37th National Meeting of the Chemical Society of Japan.
CHAPTER VIII	unpublished results.